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A REVIEW ON: - PHARMACOTHERAPY OF DIABETES MELLITUS

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ABSTRACT

Diabetes mellitus (DM) is a major public health issue affecting more than 400 million people worldwide. This metabolic disorder progressively leads to chronic microvascular, macrovascular and neuropathic life threatening complications. DM is caused either by deficiency of insulin secretion, damage of pancreatic β cell or insulin resistance related to non-use of insulin. Inclination to sedentary lifestyle may be the major reason for the continual rise in the number of diabetic patients globally which is expected to strike 366 million in 2030 in the elderly population (>65 years). Type 1 DM and type 2 DM are the 2 types of DM. Type 1 DM is an autoimmune disorder that affects pancreatic cells which reduces or impairs the production of insulin while type 2 DM is a result of impairment of pancreatic beta cells that hinder the individual's ability to use insulin. The major conventional classes of drugs for the treatment of hyperglycemia includes sulfonylureas (enhance release of insulin from pancreatic islets); biguanides (reduces hepatic glucose production); peroxisome proliferator-activated receptor-γ (PPARγ) agonists (boosts the action of insulin); α-glucosidase inhibitors (interferes with absorption of glucose in the gut).These classes of drugs are either administered as monotherapy or given in combination with other hypoglycaemics.

Severe hypoglycemia, weight gain, lower therapeutic efficacy owing to improper or ineffective dosage regimen, low potency and altered side effects due to drug metabolism and lack of target specificity, solubility and permeability problems are the major drawbacks associated with the use of the above mentioned conventional drugs. This review explores the current conventional drugs used in the treatment of type 2 DM.

KEYWORDS: Type I Diabetes Mellitus, Type II Diabetes Mellitus, Pathophysiology, Insulin, Oral Antidiabetics.

INTRODUCTION

Diabetes Mellitus (DM) is a multi-factorial chronic health condition triggered by several genetic and/or environmental factors. The disease is characterized by high blood sugar levels, due to a deficiency of concentration and/or of activity of insulin, the pancreatic hormone involved in managing glycaemia. There is no cure for diabetes so far, but it can be treated and controlled. Pharmacological therapy and/or insulin may be required in order to maintain the blood glucose level as near as possible to normal and to delay or possibly to prevent the development of diabetes-related health problems. However, disease management can be helped also by healthy eating and physical exercise.

1. Type I Diabetes Mellitus (insulin dependent Diabetes Mellitus): due to autoimmune β-cell destruction, usually leading to absolute insulin deficiency;
2. Type II Diabetes Mellitus (noninsulin dependent Diabetes Mellitus): due to a progressive loss of β -cell insulin secretion frequently on the background of insulin resistance;
3. Gestational diabetes mellitus (GDM): diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt prior to gestation;
4. Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young (MODY)), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation).

Pathophysiology of Diabetes

The homeostasis of glucose in the body is maintained by a number of hormones. However two hormones namely, insulin and glucagon play a dominant role in the regulation of glucose homeostasis. Insulin is secreted by β cells when the concentration of glucose rises. Insulin decreases the level of blood glucose either;

a) By inhibiting the production of glucose from liver by glycogenolysis and gluconeogenesis, or

b) By increasing the uptake of glucose by liver, muscle and fat tissue

Glucagon is secreted by α cell of pancreas when the concentration of glucose is low. Glucagon acts by

a) Antagonizing the effect of insulin by enhancing the processes like glycogenolysis and gluconeogenesis in liver.

b) In addition to glucagon, cortisol and catecholamines also increases the plasma glucose levels.

Other hormones which are involved in maintenance of normal glucose level are amylin (a 37 amino acid peptide), glucagon like Peptide – 1 (GLP-1) (a 30 amino acid peptide) and Glucose dependent insulinotropic polypeptide (GIP) (a 42 amino acid peptide).

Amylin is secreted along with insulin. It decreases gastric emptying, which enhances glucose absorption after a meal intake. GLP and GIP are incretin or peptide derived from the gut. These incretins facilitates the synthesis and secretion of insulin from β cells of pancreas.

Glucose is not absorbed from intestine or by cells requiring energy freely. So the distribution of glucose to the cells is done by glucose transporters. The Glucose transporters are a family of membrane bound glycoproteins and are classified into two types: -

i) Sodium glucose co-transporter (SGLT)

ii) Facilitative glucose transporter (GLUT)

Pathophysiology of T2DM may include any one or combination of any mechanisms of "ominous octet" as represented in Fig. 1 and as outlined below

BLOOD SUGAR LEVEL

	Fasting	**Just ATE**	**3 hours after eating**
Normal	80-100mg/dl	170-200	120-140
Pre- diabetic	101-125	190-230	140-160
Diabetic	126+	220-300	200+

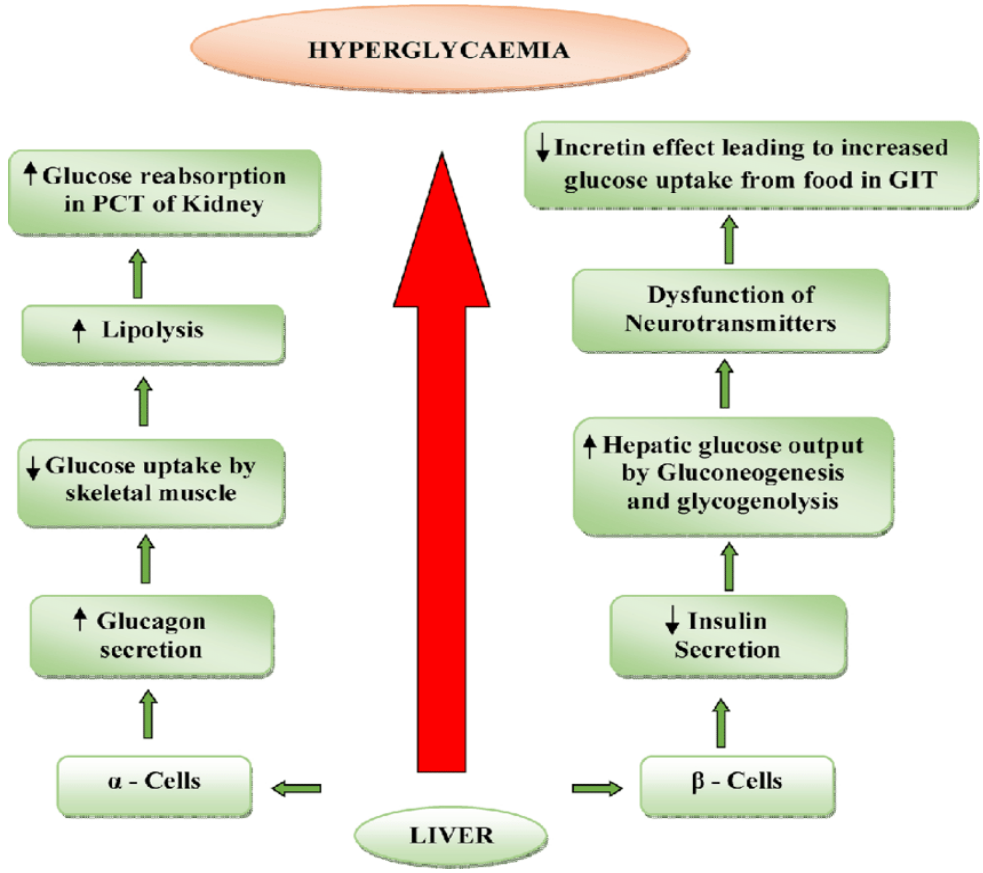


Fig. 1: Pathophysiology of T2DM – Ominous octet.

INSULIN

The chemical structure of insulin was determined by Sanger in 1951. It is a polypeptide with a molecular weight of about 6000, consisting of o amino acid chains, A and B, linked by two disulfide bridges. The chains contain 21 and 30 amino acids respectively (fig.2). Insulin was earlier obtained from bovine and porcine pancreas.

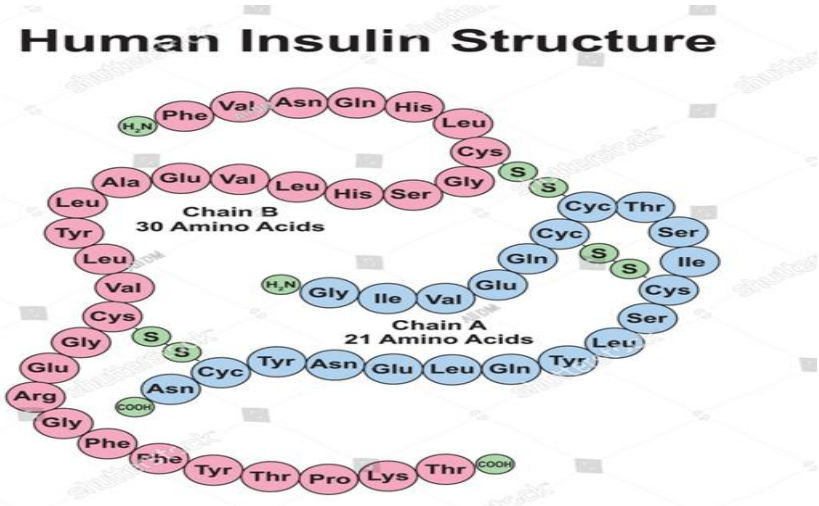


Fig.2. Structure of Insulin

Insulin biosynthesized by cultures of bacteria (E. coli) and yeasts (recombinant DNA or rDNA insulin) is now used in practice. Its primary structure (amino acid sequence), but not the secondary and tertiary structures, is identical with that of insulin derived from human pancreas. Synthetic, Modified, human rDNA insulin analogues (lispro, aspart, glargine, etc.) have different pharmacokinetic but the same pharmacodynamic properties as the native human insulin.

Insulin is soluble in water but undergoes molecular aggregation to hexameric form at extremes of pH (3.2 and 10). Such aggregation is further enhanced by zinc which brings about its crystallization. Insulin is relatively insoluble at the pH range of 4 to 7.

Synthesis and storage: The islets constitute 1% by weight of the pancreas. They contain:
Alpha or A cells which secrete glucagon.
Beta or B cells which secrete insulin.
Delta or D cells which secrete somatostatin;
And PP or F cells which secrete pancreatic polypeptide (PP)

Insulin is synthesized within the beta cells as a single chain polypeptide precursor called preproinsulin which is converted to proinsulin. Proinsulin is biologically only 1/8th as active as insulin. It is not stored but is soon cleaved by proteolytic enzymes to form the single chain C peptide and double chain insulin, which is stored in the granules of beta cells.

The pancreas of a normal human adult contains about 200 units (8 mg) of insulin. It secretes about 50 units of insulin in 24 hours, which enters the portal vein and passes to the liver. Of this, about 50% gets degraded. The remaining enters the systemic circulation. About half of the total daily insulin output is released at a slow rate, in repeated pulses, to provide a basal plasma insulin level; the other half is secreted after meals. The plasma level of insulin fluctuates throughout the day with peaks after meals.

Factors determining insulin release

Glucose: Glucose enters the beta cells via the 'glucose transporters (GULT-2). It is metabolised in the beta cells, raising the ATP/ADP ratio. As a result, the ATP sensitive K^+ channels (KATP channels) in the cell membrane close, causing its depolarisation. When the depolarisation reaches a threshold value, the Ca^{++}channels open, causing an influx of calcium into the cell. The elevated cytoplasmic calcium brings about exocytosis of the insulin

granules. The sensitivity of this insulin-releasing mechanism to glucose is dependent upon the prior carbohydrate intake. It is markedly depressed by restriction of dietary carbohydrate and fasting. Further, chronic hyperglycemia may cause selective unresponsiveness of beta cell to glucose.

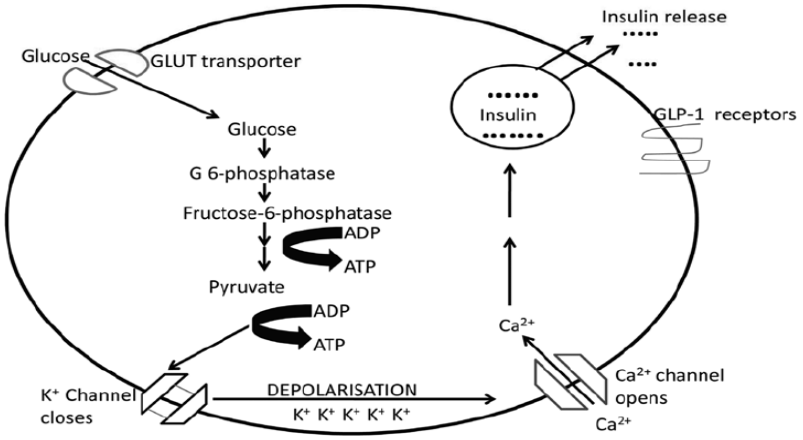


Fig. 3: Insulin Release Mechanism.

Other substrates: - Amino acids, especially arginine, fatty acids, ketones and non-glucose sugars (fructose, mannose and ribose) also stimulate insulin synthesis and release.

Gut hormones: - Ingestion of glucose or a meal causes release of the following into the portal circulation:

a. GLP-1 and GIP: Glucagon-like peptide-1(GLP-1) and glucose-dependent insulinotro- pic polypeptide (GIP) are collectively termed as incretins.

b. Pancreatic hormones, insulin and glucagon.

They modulate the plasma glucose level postprandially. GLP-1 and GIP accelerate and potentiate the glucose-mediated release of insulin from the pancreatic beta cells. This explains the larger and more prolonged insulin response to ingested than to IV glucose (Incretin effect). GLP-1 receptors are also present in brainstem nuclei involved in appetite regulation.

Other hormones: Glucagon, GH, thyroxine, ACTH and glucocorticoids also stimulate insulin release, while somatostatin, adrenaline, nor- adrenaline and exogenously administered insulin inhibit it.

Mechanism of action of Insulin

There is no single action of insulin which accounts for its diverse effects. Insulin affects all aspects of energy metabolism. It binds to specific insulin receptors present on the surface of T cells. The main target sites are the adipose tissue, the liver, and the skeletal muscles. The insulin receptor target comprises two subunits:

1. The extracellular alpha subunit which serves as the recognition site; and
2. The transmembrane beta subunit which contains the tyrosine kinase.

Binding of insulin to the receptors activates tyrosine kinase, which gets phosphorylated. Tyrosine kinase phosphorylates insulin receptor substrate 1 (IRS1). The IRS1 then phosphorylates other protein substrates in the cell, thus initiating a cascade effect. Such phosphorylation activates some enzymes while it inactivates others. The cascade is responsible for multiple (pleotropic) effects of insulin; Immediate effects on carbohydrate, lipid and protein metabolism.

Pharmacological actions of insulin: It modifies various metabolic processes in a dose-dependent manner. Thus, it:

1. Inhibits lipolysis at low plasma concentration (1-20 micro units per ml)
2. Higher levels of 10-50 micro units/ml are needed to suppress hepatic glucose production.
3. Still higher levels (30-500 micro units/ml) stimulate peripheral glucose uptake by muscle and adipose tissue.
4. Increased transport of potassium into cells requires even higher levels of plasma insulin, such as are achieved during IV glucose-insulin drip in the treatment of hyperkalemia.

Currently Available Human Insulins

1. Standard Recombinant (SR) insulins

a. Rapid acting Regular (Actrapid);

b. Intermediate acting (NPH, Insulatard);

c. Premade mixture of (a) and (b) (Mixtard),

2. Human Insulin analogues, recombinant

a. Very Rapid Acting (VRA): Lispro: (Humalog). Aspart (Novolog), Glulisine (Apidra)

b. Intermediate acting premade mixtures, Lispro-prot amine + Lispro (Humalog Mix): Aspart-protamine +Aspart (Novolog Mix)

c. Long acting insulins: Glargine (Lantus); Detemir (Levemir)

d. Ultra-long acting insulin: Insulin Degludec

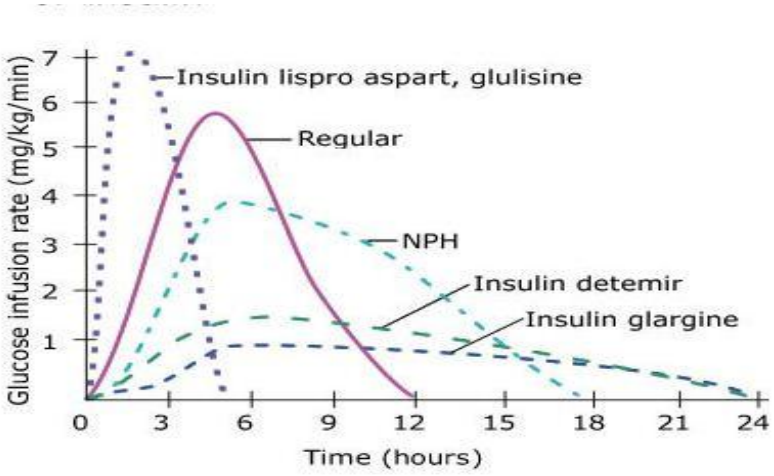


Fig. 4: Extent and duration of action of various types of insulin.

Adverse Reaction of Insulin

"Hypoglycemia: Hypoglycemia is a common adverse effect of insulin. It is less frequent with rapid and long acting analogs than with regular insulin and NPH respectively. The common causes of hypoglycemia are:

a. Too large a dose;

b. Failure to eat;

c. Vigorous physical exercise, and

d. Ingestion of alcohol.

Oral Antidiabetic Drugs

- **Sulfonylureas**
  - **First Generation:** - Acetohexamide, Chlorpropamide, Tolazamide, Tolbutamide.
  - **Second Generation**: - Glibenclamide, Glipizide, Gliclazide, Glimepiride.
- **Meglitinide**
  - Rapaglinide
  - Nateglinide
- **Dipeptidyl peptidase-4 inhibitors**
  - Sitagliptin
  - Linagliptin
  - Vildagliptin
  - Saxagliptin

- Teneligliptin
- Alogliptin

➢ **Alpha Glucosidase 4 inhibitors**

- Voglibose
- Miglitol
- Acarbose

➢ **Biguanide**

- Metformin
- Phenformin
- Buformin

➢ **Thiazolidinedione**

- Pioglitazone
- Rosiglitazone

➢ **Miscellaneous**

i) Sod. Glucose cotransport-2 (SGLT-2) inhibitor: - Dapagliflozin, Canagliflozin

ii) Dopamine D2 agonist: - Bromocriptine

Drug	Preparations	Plasma $t_{1/2}$ (hr)	Duration of action (hr)	Clearance route	Daily dose	No of doses per day	Remarks
SULFONYLYREASE							
Tolbutamide	RASTINON ,0.5gm tab	6	6-8	L	0.5-3g	2-3	Weaker, shorter acting, flexible dosage, safer in elderly and in those prone to hypoglycemia.
Glibenclaimide	DAONIL, EUGLUCON, BETANASE 2.5,5.0mg Tablet	2-4	24	L	2.5-15 mg	1-2	Potent but slow acting, higher incidence of hypoglycemia, single daily dose despite short 1½ due to active metabolite and sequestration in beta cells.
Glipizide	GLYNASE, GLIDE, MINIDIAB, 5 mg tablet	3-5	12	L	5-20 mg	1-2	Fast and shorter acting, higher daily dose to be divided, hypoglycemia and

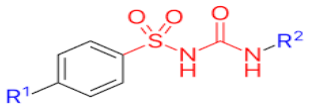
							weight gain less likely, preferable in elderly.
Gliclazide	DIAMICRON80 mg tablet , DIAZIDE 20,80 mg tablet GLIZID 30,40,80 mg tablet	8-20	12-24	L	40-240 mg	1-2	Has antiplatelet action, generates only inactive metabolite, daily dose > 80 mg to be divided.
Glimepride	AMARYL, GLYPRIDE , GLIMER 1,2 mg tablet	5-7	24	L	1-6 mg	1-2	Long acting, only inactive metabolite, Stronger extra-pancreatic action.
MEGLITINIDE							
Repaglinide	EUREPA, RAPLIN, NOVONORM, REGAN 0.5,1,2,mg tablet	<1	3-5	L	1-8 mg	3-4	Given ½ hr before each meal for limiting post-prandial hyperglycaemia.
Nateglinide	GLINATE, NATELIDE, 60,120 mg tablet	1.5	2-3	L	180-480 mg	3-4	Stimulates 1st phase insulin secretion, less likely to cause delayed hypoglycaemia.
DIPEPTIDYL PEPTIDASE-4 INHIBITORS							
Sitagliptin	JANUVIA 50,100 mg tablet	12	24	K	100 mg	1	Non-covalent binding to DPP-4; excreted unchanged in urine. Low risk of hypoglycemia. Body weight neutral.
Vildagliptin	GALVUS, JALARA, ZOMELIS 50 mg capsule	2-4	12-24	L,K	50-100 mg	1-2	Covalent binding to DPP-4; Metabolized in liver: Hepatotoxicity reported.
BIGUANIDE							
Metformin	GLYCIPHAGE, GLYCOMET 0.5 , 0.85 g tab 0.5 g and 1.0 g SR tab	1.5-3	6-8	K	0.5-2.5 gm	1-2	No hypoglycemia. Not metabolized. Lactic acidosis rare and only in kidney disease.
THIAZOLIDINE DIONE							
Pioglitazone	PIONORM ,	3-5	24	L	15-45	1	May improve lipid

	PIOREST , PIOZONE 15,30 mg tab				mg		profile. Reverses insulin resistance. No hypoglycemia, C/I in liver and heart disease.

*L- metabolized in liver; K – Excreted unchanged by kidney

1. Sulfonylureas

Sulfonylureas are the oldest class of oral ant diabetic medication dating back to the 1950s. All sulfonylureas contain a phenyl-sulfonyl-urea structure, which exerts the hypoglycemic effect. Patients with type II diabetes mellitus use sulfonylureas as monotherapy or in combination with other oral or injectable medications.



Mechanism

Sulfonylureas bind to and inhibit the ATP-sensitive potassium channels (K) on the pancreatic beta cells. As a result, potassium efflux decreases, and the beta-cell membrane depolarizes. Membrane depolarization causes calcium channels to open, leading to calcium influx and increased intracellular calcium, which stimulates insulin secretion from the pancreatic beta cells.

Pharmacokinetics

Sulfonylureas are well absorbed after oral administration. Glipizide absorption is delayed by food. All sulfonylureas are highly bound to plasma protein (90% to 99%). Plasma protein binding is least for Chlorpropamide and greatest for glyburide. Sulfonylureas are metabolized in the liver and excreted in the urine

ADR of Sulfonylurea

Hypoglycemia

Hypersensitivity reactions

Other adverse effects of sulfonylureas include nausea and vomiting, occasional hematologic reactions (especially leukopenia and thrombocytopenia, and hemolytic anemia in susceptible patients), cholestatic jaundice, and dermatologic effects. Sulfonylureas are teratogenic in animals (large doses). Patients taking sulfonylureas tend to gain weight, which is a problem in type 2 diabetics, who tend to be obese.

Sulfonylureas have a disulfiram-like effect.

Glimepiride

Glimepiride is a newer, novel second generation Sulphonylurea. It increases insulin secretion by stimulating beta cells and also has significant extra pancreatic activity.

1. Beta Cell Action

Glimepiride binds to a specific receptor site 65 KDs region in the beta cell while Glibenclamide binds to 140 KDs region. Glimepiride binds to its receptor 2.5 to 3 times faster and dissociates from it binding site 8 to 9 times greater than Glibenclamide.

The mechanism of insulin secretion and release is similar to Glibenclamide ie. Via the closure of ATP dependent potassium channel and opening up of voltage dependent calcium channel and increase of intracellular calcium concentration leading to exocytosis of insulin. Sulphonylureas act at the level of potassium – ATP channel.

However current Sulphonylureas may not stimulate beta cells in a controlled fashion or in proportion to the blood glucose level, because of their fixed blocking of potassium-ATP channel. Agents that accomplish this in a more flexible fashion may lead to less secondary failure. Glimepiride which binds to a different portion of Sulphonylurea receptor, leading to less fixed blockage of potassium-ATP channel may have less secondary failure. The amount of insulin secretion is more or equivalent to that of Glibenclamide but the secretion with glimepiride is very quick and lasts for a short time than Glibenclamide and hence there will be no hyperinsulinism and reduced likelihood of in-between meal hypoglycemia.

2. Insulin-independent blood glucose decreasing activity of Glimepiride

Glimepiride exhibits a more pronounced insulin independent blood glucose decreasing activity compared to glibenclamide. This can be explained by stimulation of glucose transport and nonoxidative glucose metabolism and adipose tissue and muscle cells. The increased glucose transporter activity is brought out by increased translocation of GLUT-4 isoform from inside the cell to surface of adipocytes and muscle. It increases insulin sensitivity and decreases insulin resistance. If hyperinsulinemia is a concern in therapy of Type 2 diabetes, the higher insulin-independent blood blood glucose decreasing activity of glimepiride might be of therapeutic relevance.

Dosage and Administration

Glimepiride is indicated in Type 2 diabetics when diet and exercise fails. Dosage is individualised for each patient so as to achieve and maintain satisfactory blood glucose level at a minimum effective dose. The fasting blood glucose andHbA1c measurements should be performed periodically.

The usual starting dose of glimepiride is 1 mg. Maximum initial dose 2 mg once daily taken just before breakfast or with the first main meal of the day. Further increments can be made at 1 or 2 week intervals in increments of 2 mg.

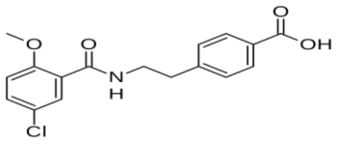
The patient's blood glucose response should guide dosage titration. The usual maintenance dose is 1 to 4 mg once daily. Maximum recommended dose is 8 mg once daily. There is no need to split the dosage to twice daily.

Once daily dosage will improve patient's compliance.

2. Meglitinide

Meglitinides or glinides are a class of drugs used to treat type 2 diabetes.

In the late 1970s, a compound was developed by the addition of a COOH group to the non-sulfonylurea end of the Glibenclamide molecule (later called Meglitinide). It was shown to be hypoglycemic action through blockade of K^+ATP channel and augmentation of insulin secretion Henquin (1990). Unlike the sulfonylurea drug Glibenclamide, it has similar binding affinity for the different sulfonylurea receptors SUR1 (the predominant form in the pancreatic islet beta-cell and neurons), SUR2A (the predominant form in heart and skeletal muscle), and SUR2B (the predominant form in smooth muscle) Meyer et al (1999).



Mechanism of Action

They bind to an ATP-dependent K^+ (KATP) channel on the cell membrane of pancreatic beta cells in a similar manner to sulfonylureas but have a weaker binding affinity and faster dissociation from the SUR1 binding site. This increases the concentration of intracellular potassium, which causes the electric potential toward the intracellular side of the membrane to become more positive. This depolarization opens voltage-gated Ca2+ channels. The rise in

intracellular calcium leads to increased fusion of insulin granula in the cell membrane, and therefore increased secretion of (pro) insulin.

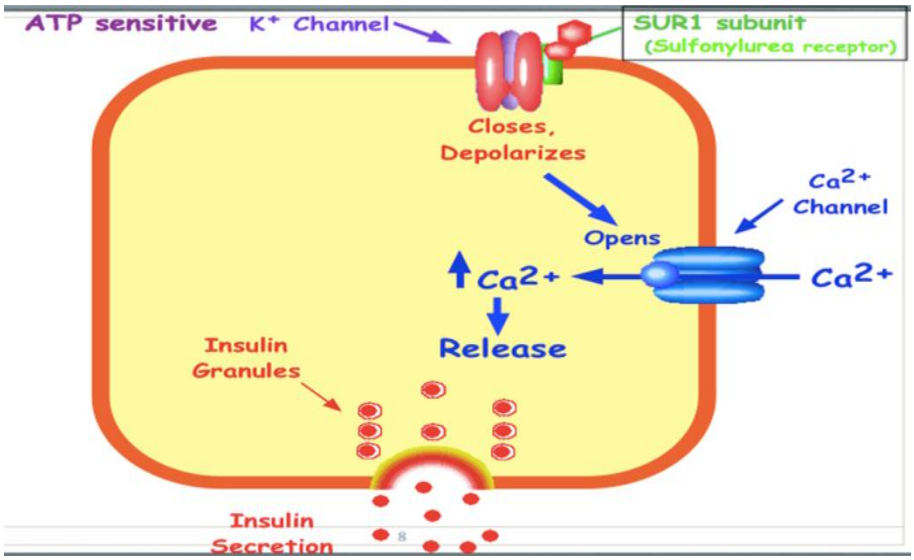


Fig: Mechanism of action of meglitinides.

Repaglinide

Repaglinide is a non-sulphonylurea antidiabetic agent and a short acting insulin secretagogue. It is a benzoic acid derivative and is an analog of meglitidine family.

The meglitidine shares the non-sulphonylurea moiety of glibenclamide.

Mode of action

Repaglinide has a unique binding site on beta cell, different from that of glibenclamide. It acts via closure of ATP dependent K^+ channel in beta cell. It is 3 to 5 times more potent insulin releaser than glibenclamide but its action is short lived. It is metabolized in the liver and secreted in bile.

Repaglinide vs Glibenclamide

When compared to glibenclamide, Repaglinide has the following characteristic feature:

1. Fast Absorption
2. Short biological half life
3. Short duration of insulinotrophic activity
4. Lowest post-prandial Blood glucose
5. No in-between meal hypoglycaemia or hyperinsulinemia

Uses

a) Primary Therapy in Type 2 Diabetes

Repaglinide is a prandial glucose regulator. It has a fast onset and short duration of action. The initial dose is 0.5 to 1 mg and gradually increased upto 2 to 4 mg. It should be administered three times a day just, before along with or immediately after a meal and offers greater flexibility in meal times and drug dosing.

b) Useful in patients who eat at irregular times or miss a meal

Repaglinide increases insulin secretion sufficient to control the post meal surge and not for so long as to produce hypoglycaemia in-between meals and especially when a meal is missed or delayed as is the case with long acting insulinotrophic agents. So, there is no in-between meal hypoglycaemia.

3. Dipeptidyl peptidase-4 inhibitors

Dipeptidyl peptidase 4 (DPP-4) inhibitors are a group of antihyperglycemic medications used to manage type 2 diabetes mellitus, DPP-4 inhibitors, known as gliptins, approved by the Food and Drug Administration (FDA). Apart from antihyperglycemic effects, this class of drugs possesses antihypertensive effects, anti-inflammatory effects, antiapoptotic effects, and immunomodulatory effects on the heart, kidneys, and blood vessels independent of the incretin pathway.

Mechanism of Action

DPP-4 is a ubiquitous enzyme that acts on incretin hormones, mainly GLP-1 (glucagon-like peptide-1) and GIP (gastric inhibitory peptide), which maintain glucose homeostasis by increasing insulin secretion and decreasing glucagon secretion.

GLP-1 is a hormone secreted by enters endocrine L cells of the small intestine, which lowers blood glucose by stimulating insulin secretion, reducing glucagon concentrations, and delaying gastric emptying.

Administration

All the DPP-4 inhibitors are administered orally, once daily, before or after meals. A study of oral and intravenous administration of Sitagliptin in healthy individuals demonstrated an 87% oral bioavailability

Adverse Effects

Gliptins are associated with a low incidence of adverse events, including hypoglycemia, and have weight-neutral effects. However, the risk of hypoglycemia increases when used in conjunction with sulfonylureas. The most common side effects noticed with the DPP-4 inhibitors Sitagliptin and Saxagliptin are upper respiratory tract infection (URTI), nasopharyngitis, headache, urinary tract infection, and arthralgia.

4. Biguanide

The biguanides are derivatives of the compound biguanide (guanylguanidine) that exert a blood glucose-lowering effect in type 2 (non-insulin dependent) diabetes mellitus. The main biguanides are metformin (dimethylbiguanide) and phenformin (phenethylbiguanide), which were described in 1957 and buformin (butylbiguaninde), which was described in 1958 Schafer (1983), Bailey (1992). Phenformin and buformin were withdrawn from clinical use in most countries in the late 1970s due to a high incidence of associated lactic acidosis. Metformin, which has a much lower risk of lactic acidosis, is used widely in the treatment of type 2 diabetes.

Mechanism of Action

All biguanides display an inhibitory effect on complex I and inhibit the rate of oxygen consumption, thereby causing energy stress, increase in AMP/ATP ratio, and activation of AMP Kinase (AMPK),

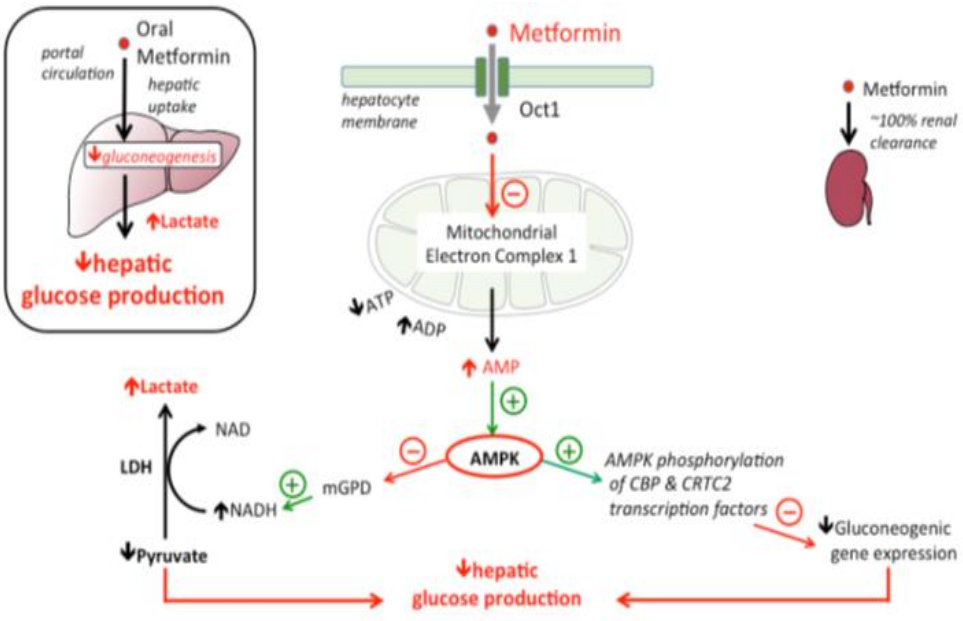


Fig. Mechanism of action of biguanide

ADR

The most common side effect is diarrhea and dyspepsia, occurring in up to 30% of patients. The most important and serious side effect is lactic acidosis, therefore metformin is contraindicated in advanced chronic kidney disease. Kidney function should be assessed before starting metformin. Phenformin and buformin are more prone to cause acidosis than metformin.

5. Thiazolidinedione

The use of thiazolidinediones, also called "glitazones," in managing type 2 diabetes can help with glycemic control and insulin resistance. There are two thiazolidinediones, rosiglitazone, and pioglitazone, currently approved by the FDA as monotherapy or combined with metformin or sulfonylureas to manage type 2 diabetes mellitus. These medications should be in conjunction with lifestyle modifications such as diet, exercise, and weight reduction. Thiazolidinediones may also be used to treat polycystic ovarian syndrome, as these may lead to improved endothelial function, improved ovulation, and reduction of insulin resistance.

Thiazolidinediones (TZDs) are taken orally once daily, with or without food. Before initiating treatment and periodically during therapy, LFTs and HbA1C levels require monitoring.

Mechanism

The thiazolidinediones increase insulin sensitivity by acting on adipose, muscle, and, to a lesser extent, liver to increase glucose utilization and decrease glucose production. TZDs function by regulating gene expression through binding to peroxisome proliferator-activated receptor-gamma (PPAR-gamma), a nuclear transcription regulator.

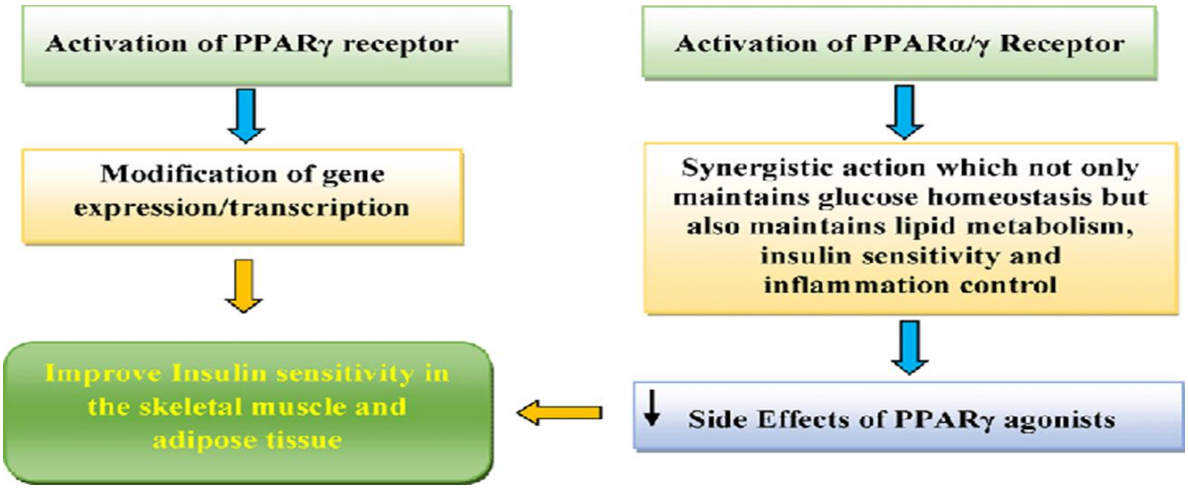


Fig. Mechanism of action of thaizolidine diones.

ADR

There are several undesirable side effects to thiazolidinedione's, particularly with long-term use.

Edema and Congestive Heart Failure

TZDs have been shown to cause dose-related fluid retention in up to 20% of patients. Methods of fluid retention include PPAR-gamma receptors in the distal nephron and insulin-activated epithelial sodium channels in the collecting tubules. PPAR-gamma activation stimulates sodium reabsorption, acting at the same site as aldosterone. Patients with preexisting edema or concomitant insulin therapy are at higher risk of edema and should start on the lowest available dose.

Weight Gain

Adipocytes have the highest concentration of PPAR-gamma receptors in the body. The mechanism behind the weight gain is due to a combination of factors. TZDs up regulate PPAR-gamma receptors in the central nervous system, leading to increased feeding. TZD agents expand adipose tissue mass via the maturation of preadipocytes into mature adipocytes and increase fat storage by increasing free fatty acid movement into cells. Additionally, fluid retention can increase weight.

Bladder Cancer

Pioglitazone has, in some studies, shown correlations with an increased risk of bladder cancer. This effect varies in a duration-dependent and dose-dependent fashion. Also, most recent analyses do not support an increased risk. In contrast, rosiglitazone was not associated with an increased risk of bladder cancer in any analysis, suggesting the risk is drug-specific and not a class effect.

Hepatotoxicity

Troglitazone, the original PPAR-gamma activator, was removed from the market primarily due to hepatotoxicity.

Diabetic Macular Edema

Combination TZD and insulin therapy have correlated with an increased incidence of diabetic macular edema at 1-year and 10-year follow-up.

Increased Ovulation and Teratogenic Effects

Patients with polycystic ovarian syndrome have shown an increased ovulation rate when using TZD and other insulin sensitizers.

6. Alpha-Glucosidase inhibitors

In human salivary amylase, pancreatic amylase and alpha-glucosidase are the enzymes involved in the digestion of starch. All complex carbohydrates like starch and sucrose have to be converted to simple carbohydrates in the small intestine by an enzyme alpha-glucosidase before absorption.

Drugs which inhibit the action of alpha-glucosidase known as glucosidase inhibitor, preventing the breakdown of complex carbohydrates thereby delay or preventing carbohydrate absorption. Glucosidase inhibitors are three types:

1. Reversible competitive inhibitors of alpha glucosidase. eg: a. Acarbose; b. Meglital
2. Irreversible glucosidase inhibitor eg: Gasternospermine.
3. Powerful Sucrose inhibitor eg: Veglibose.

Acarbose is freely available for clinical use. Other drugs are under clinical trial.

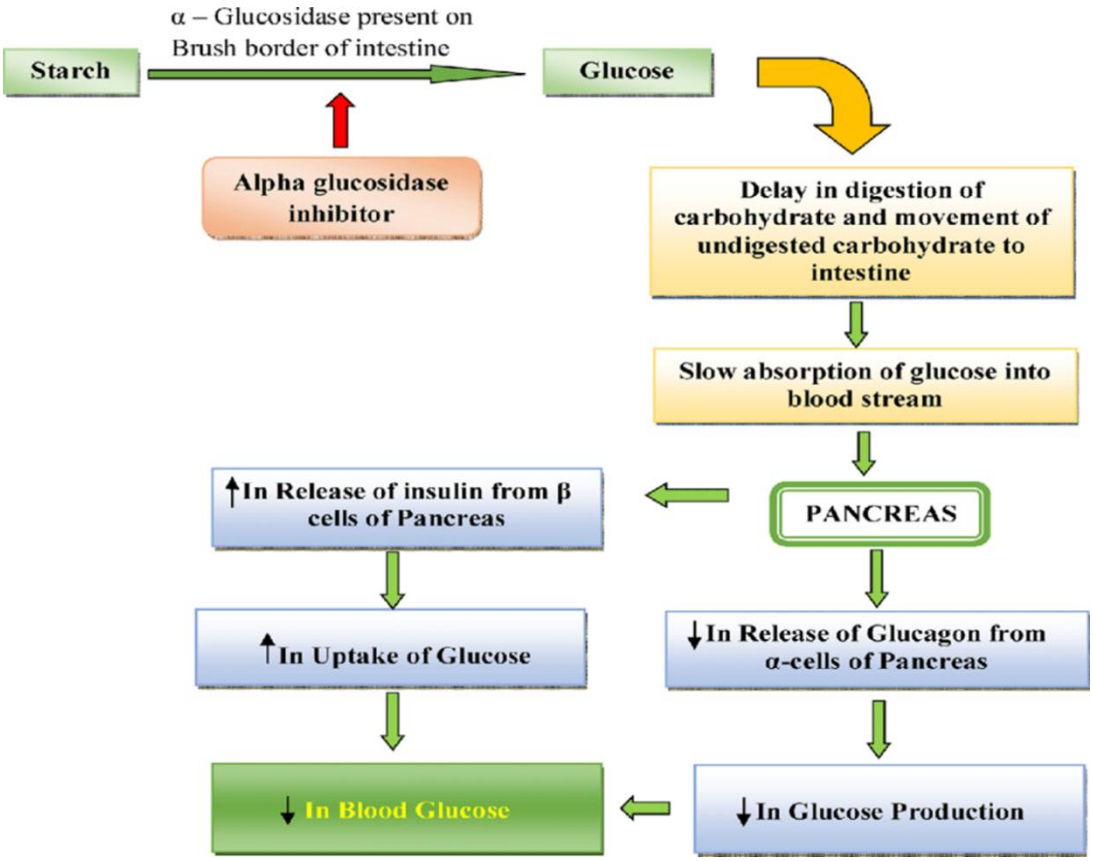


Fig. Schematic mechanism of α – glucosidase inhibitor to lower the blood glucose level.

Acarbose

Mode of Action

1. Acarbose blocks the digestion of starch, sucrose and maltose. The digestion of carbohydrate is delayed and occurs throughout the small intestine, rather than upper part of jejunum. Absorption of glucose and other monosaccharides in not affected. The net result is a decrease in post prandial rise in blood glucose. Most of the carbohydrate is eventually absorbed and that which is now absorbed is metabolised by the bacteria in the colon to short chain fatty acids which are then absorbed in the colon. 2. Acarbose decreases meal stimulated secretion of gastric inhibitory polypeptide and other gastrointestinal peptide (inhibitors) hormones. There is smaller increase in post prandial blood sugar level that leads to smaller increase in insulin level. 3. Acarbose does not cause weight gain with the therapeutic doses.

Side Effects

Abdominal fullness, borborygmi, increased intestinal flatulence and diarrhoea are major side effects of alpha-glucosidase inhibitors. These side effects are due to undigested sugars passing through large bowel where bacterial fermentation occurs, producing both carbondioxide and large quantities of osmotically active glucose load, leading to diarrhoea and flatulence. These symptoms occur in the first few weeks of treatment and abate with continued long term treatment.

Uses

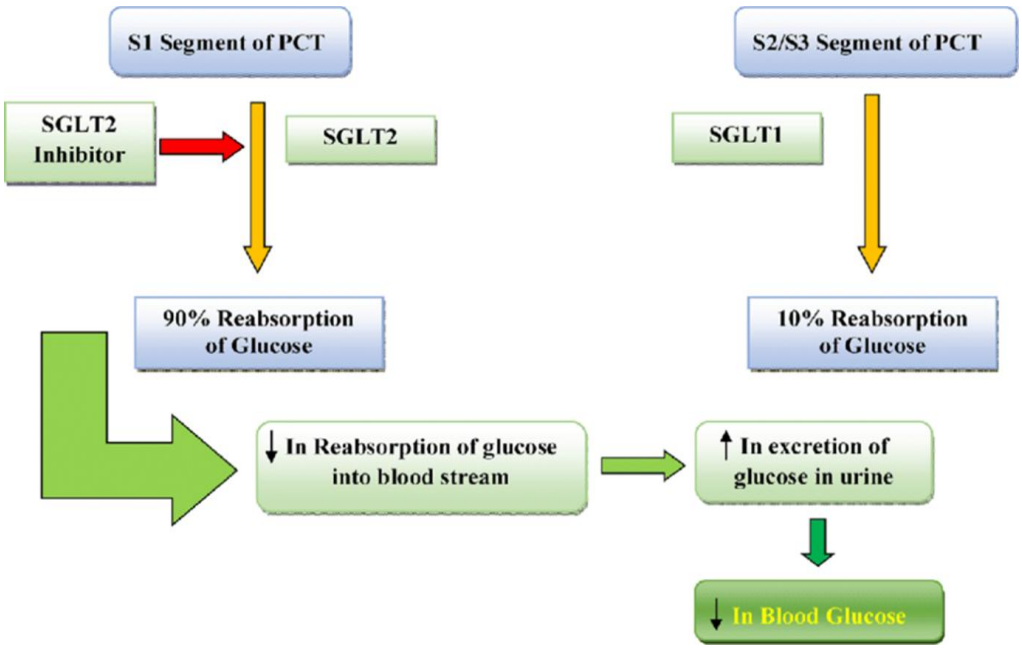
In non-diabetics and in Type 2 diabetics acarbose produces a dose related decrease in post-prandial hyperglycemia. Acarbose therapy causes a corresponding reduction in post prandial plasma insulin response. Long term treatment either as mono-therapy or in combination with S.U, acarbose improves basal blood sugar concentration as well. Thus insulin resistance decreases and sensitivity improves consequent to reduction in hyper-glycaemia. In IDDM: Long term treatment with acarbose reduces both post prandial and basal hyper glycaemia and reduces insulin requirement by 10 to 30 % interestingly, episodes of hypo-glycaemia between meals may be less frequent and less severe in IDDM.

In treatment of hypoglycemia in patients taking acarbose, only oral or IV (glucose) should be given.

Sucrose and other complex carbohydrates should not be used.

7. Sodium glucose co-transporter 2 antagonists/ inhibitors

Reabsorption of glucose in proximal convoluted tubule (PCT) is achieved by passive transporter, facilitative glucose transporter (GLUT) and active co-transporter, sodium glucose co-transporter (SGLT). SGLT2 inhibitors inhibit the SGLT2 present in PCT which prevents reabsorption of glucose and enhances the excretion of glucose in urine. As glucose is excreted in urine, the glucose level in the blood is maintained and other glycaemic parameters are maintained. The available molecules in this category are Canagliflozin, Dapagliflozin, Empagliflozin, Ipragliflozin, Luseogliflozin and Tofogliflozin. SGLT2 inhibitors are used in monotherapy or in combination with metformin, sulfonylurea or thiazolidinedione's or as add on with insulin.



Schematic representation of mechanism of action of SGLT2 Inhibitors.

CONCLUSION

Diabetes mellitus is a serious complication in today life. Diabetes mellitus is caused by insufficient or inefficient production of insulin by the pancreas, causing an imbalance (increase or decrease) in blood glucose levels. The lifestyle and day today circumstances are play major role in occurring this type of serious complications. In this review we get some idea regarding diabetes mellitus and pharmacotherapy of diabetes mellitus.

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