ANTI-DIABETIC DRUGS

Pancreas is both an endocrine gland that produce insulin, glucagons and somatostatin and exocrine gland that produce digestive enzymes.

These hormones play an important role in regulating the metabolic activities of the body, particularly the homeostasis of blood glucose. Examples: Hyperinsulinemia (due to an insulinoma) can cause severe hypoglycemia. A relative or absolute lack of insulin, in diabetes mellitus, can cause serious hyperglycemia.

Insulin Hormone consist of 2 peptide chains that are connected by disulfide bonds It is synthesized as a precursor (pro-insulin) that undergoes proteolysis to from insulin and C peptide, both of which are secreted by the β cells of the pancreas. Measurement of circulating C peptide provides a index of insulin levels.

Mechanism stimulated insulin secretion Hyperglycemia results in increased intracellular ATP levels, which close the ATP-dependent potassium channels. Decreased outward potassium efflux results in depolarization of the beta cell and opening of voltage-gated calcium channels. The resulting increased intracellular calcium triggers secretion of the hormone.

Metabolic effects of insulin Carbohydrate metabolism: In liver, inhibits gluconeogenesis and glycogen breakdown In muscle and liver, increases glycogen synthesis In muscle and adipose tissue (& other tissues), increases glucose uptake by increasing number of glucose transporters in the cell membrane Overall effect is to decrease glucose concentration in plasma.

Effects on carbohydrate metabolism: About half of ingested glucose is utilized to meet energy demand through the process of glycolysis, the other half is either converted to fat40% or glycogen 10%.

Diabetes mellitus

 Diabetes mellitus, affecting 171 million people worldwide as of 2000, a number expected to be more than double, up to 366 million, by 2030. The majority 90% have T2DM, which is linked to westernized diets, obesity, and inactivity Type 2 diabetes mellitus is a complex of metabolic condition characterized by elevated levels of serum glucose, caused mainly by impairment in both insulin action and insulin secretion.

The classification of diabetes

1. Type 1 Diabetes mellitus, it results from β-cell destruction, usually leading to absolute insulin deficiency.

2. Type 2 Diabetes mellitus, it ranges from predominant insulin resistance with relative insulin deficiency to predominant insulin secretary defect with insulin resistance.

3. Other specific types of diabetes: genetic defects of the βcells, genetic defects in insulin action, diseases of the exocrine pancreas, endocrinopathies, drug or chemical induced diabetes, infections.

4. Gestational Diabetes (GDM), it is diagnosed during pregnancy.

Treatment of Type 2 diabetes :

The goal in treating Type 2 diabetes is to: Maintain blood glucose concentrations within normal limits Prevent the development of long-term complications of the disease.

Rapid-onset and ultrashort-acting insulin Preparations

1. Regular insulin 2. Insulin lispro 3. Insulin aspart 4. Insulin glulisine.

Regular insulin It is a short-acting, soluble, crystalline zinc insulin. It is usually given subcutaneously (or intravenously in emergencies) It rapidly lowers blood sugar It is safely used in pregnancy

Insulin lispro, Insulin aspart and Insulin glulisine Classified as ultrashort-acting insulins (Because of their rapid onset and short duration of action). These agents offer more flexible treatment regimens and lower the risk of hypoglycemia Used in pregnancy only if clearly needed

Intermediate-acting insulin preparations

1. Lente insulin Its onset of action and peak effect are slower than those of regular insulin, but are sustained for a longer period. Not suitable for intravenous administration.

2. Isophane NPH insulin suspension: Neutral protamine Hagedorn insulin It is a suspension of crystalline zinc insulin combined at neutral pH with a positively charged polypeptide, protamine. Its duration of action is intermediate(due to delayed absorption of the insulin because of its conjugation with protamine, forming a lesssoluble complex). Should only be given subcutaneously It is useful in treating all forms of diabetes except diabetic ketoacidosis or emergency hyperglycemia.

long-acting insulin preparations 1. Insulin glargine The isoelectric point of insulin glargine is lower than that of human insulin, leading to precipitation at the injection site (extending its

action) It is slower in onset than NPH insulin and has prolonged hypoglycemic effect It has no peak.

2. Insulin detemir Most recently developed long-acting insulin analog. It is associated with than NPH insulin. Has a dose-dependend hypoglycemic effect. Onset of action of 1-2 hours. Duration of action of more than 24 hours. It is given twice daily.

Insulin combinations Various premixed combinations of human insulins: 70% NPH insulin + 30% regular insulin 50% NPL insulin + 50% lispro insulin 75 % NPL insulin + 25% lispro insulin

Insulin administration (not given orally, why?) It is administered by subcutaneous injection, insulin is a polypeptide (it is degraded in the gastrointestinal tract if taken orally). I.V. injection (in a hyperglycemic emergency, regular insulin) I.V. infusion (to avoid multiple injections)

 Insulin pumps (open-loop pumps): Continuous subcutaneous administration , not require multiple daily injections .The devices have a user-programmable pump that delivers individualized basal and bolus insulin replacement doses based on blood glucose self-monitoring results.

 Portable pen injectors: These contain cartridges of insulin and replaceable needles. Aerosol preparation: Inhaled insulin preparation of finely powdered ,Insulin is absorbed into the bloodstream through alveolar walls, but the challenge has been to create particles that are small enough to pass through the bronchial tree without being trapped.

Adverse reactions to insulin

1. Hypoglycemia (more common) due to over dose (tachycardia, confusion, vertigo, diaphoresis) Treatment of hypoglycemia: Conscious patient: Orange juice, glucose, Suger containing beverage, food. Unconsciousness patient (severe hypoglycemia) Intravenous infusion of 20-50 mL of 50% glucose solution over a 2-3 minute. In the absence of intravenous infusion, 1 mg of glucagon (subcutaneous or intramuscular administration) ,restore consciousness within about 15 minutes then food consumption

2. lipodystrophy Atrophy of subcutaneous fat due to availability of more highly concentrated insulin preparations of neutral pH. Hypertrophy of subcutaneous fatty tissue (if insulin is injected repeatedly at the same site)

3. Allergic reactions, and local injection site reactions Immediate type hypersensitivity, rare urticaria follows histamine release from tissue mast cells (sensitized by anti-insulin IgE antibodies) Treatment by antihistamines, corticosteroids common. 4. Weight gain 5. Insulin immune resistance Due to high titer circulating IgG anti-insulin antibodies Note: Diabetics with renal insufficiency may require adjustment of the insulin dose

Non Insulin Antidiabetic Drugs

 Insulin secretagogues 1. Sulfonylureas 2. Meglitinide analogs Insulin Sensitizers 1. Biguanides 2. Thiazolidinediones or glitazones Alpha - Glucosidase Inhibitors 1. Acarbose 2. Miglitol Amylin analog 1. Pramlintide Gastrointestinal Hormones 1. Incretins analoge (Incretins Mimetics) 2. Dipeptidyl Peptidase-4 Inhibitors(DPP-4 inhibitor)

Non Insulin Antidiabetic Drugs For treatment of patients who have Type 2 Diabetes but cannot be managed by diet alone. A combination of hypoglycemic drugs with or without insulin to control the hyperglycemia (for Patients with long-standing disease). Oral hypoglycemic agents should not be given to patients with Type 1 diabetes Note: The patient respond well to oral hypoglycemic agents if diabetes occurs after age fourty and has had diabetes less than five years

Insulin secretagogues 1. Sulfonylureas Tolbutamide (First-Generation Sulfonylureas) Glyburide, glipizide, and glimepiride (secondGeneration derivatives) Mechanisms of action of the sulfonylureas 1. Stimulate insulin release from βcells of pancreas by blocking the ATP-sensitive K+ channels, resulting in depolarization of the beta cell and opening of voltage-gated calcium channels. The resulting increased intracellular calcium triggers secretion of the hormone. 2. Reduction of serum level of glucagons 3. Increase binding of insulin to receptors

Pharmacokinetic of the sulfonylureas Given orally Bind to serum proteins Tolbutamide duration of action is 6-12 hours Second-generation agents last about 24 hours. Metabolized by liver The drugs and its metabolites excreted by kidney

Adverse effects of sulfonylureas Weight gain Hyperinsulinemia Hypoglycemia Can deplete insulin from fetal pancreas (cross the placenta), so pregnant women with type 2 DM should be treated with insulin.

2. Meglitinide analogs (repaglinide, nateglinide) They are postprandial glucose regulators (effective in early release of insulin that occurs after a meal). Their action is dependent on functioning of pancreatic B cells. They bind to distinct site of on sulfonylurea receptor of ATP-sensitive potassium channels, thereby initiating a series of reactions resulting in insulin secertion. In contrast to sulfonylureas, meglitinide has a rapid onset and short duration of action. Combinetion therapy with metformin or the glitazonesbetter than monotherapy

Pharmacokinetic of Meglitinides Well absorbed orally Taken 1- 30 minutes before meals Meglitinides are metabolized by CYP3A4 to inactive products in the liver Excreted through the bile. Adverse effects of Meglitinides Hypoglycemia (the incidence Hypoglycemia lower than that with the sulfonylureas) These agents must be used with caution in patients with hepatic impairment Weight gain is less with the meglitinides than with the sulfonylureas.

Drug interaction with Meglitinide 1. Enzyme inhibitor (ketoconazole, itraconazole, erythromycin, and clarithromycin) enhance the effect of repaglinide 2. Enzyme inducer (barbiturates, carbamazepine, and rifampin, decrease the glucose-lowering effect of repaglinide) 3. Repaglinide cause severe hypoglycemia in patients who are also taking the lipid-lowering drug gemfibrozil.

Biguanides (Metformin)

 Metformin is only available biguanide It require insulin for it is action It will increase glucose uptake and decrease insulin resistance It will not increase insulin secretion hypoglycemia is less than that with sulfonylurea agents.

Action of Metformin Reduce hepatic glucose out put (inhibiting hepatic gluconeogenesis) It slows intestinal absorption of sugars. Reduces hyperlipidemia (LDL and VLDL) cholesterol concentrations Rises HDL cholesterol These effects may not be apparent until 4 -6 weeks of use.

 Metformin may be used alone or in combination with other oral agent or with insulin It Is decrease cardiovascular mortality. The patient often loses weight because of loss of appetite Hypoglycemia has occurred when metformin was taken in combination. Note: If used with insulin, the dose of the hormone must be adjusted, because metformin decreases the production of glucose by the liver

Pharmacokinetic of metformin Well absorbed orally Not bound to serum proteins Not metabolized Highest concentration are in saliva and intestinal wall Excretion via urine

Adverse effects of metformin 1. GIT disturbance 2. Interfere with vitamin B12 absorption (Longterm use) 3. Fatal lactic acidosis (Rarely). Note: Lactic acidosis is type of metabolic acidosis caused by accumulation of lactic acid due to tissue hypoxia, drug effect, or unknown etiology.

Contraindications of metformin Renal disease Hepatic disease Cardiac or respiratory insufficiency A history of alcohol abuse Severe infection Pregnancy Drug-drug interactions Metformin may be enhanced by cimetidine, furosemide, nifedipine.

Other uses of metformin Metformin is effective in the treatment of polycystic ovary disease. Its ability to lower insulin resistance in these women can result in ovulation and, possibly, pregnancy

Thiazolidinediones or glitazones

Troglitazone withdrawn (due to hepatotoxicity) Pioglitazone Rosiglitazone They are insulin sensitizers Not promote insulin release from the pancreatic β-cells (hyperinsulinemia not

occurs) Insulin is required for their action Pioglitazone and rosiglitazone can be used as monotherapy or in combination with other hypoglycemics or with insulin

Mechanism of action of Thiazolidinediones They are target a nuclear hormone receptor, the peroxisome proliferator activated receptor (PPAR-γ) Pioglitazonehas PPAR-α as well as PPAR-γ Peroxisome proliferator-activated receptor gamma is a nuclear transcription factor which triggers the expression of multiple genes involved in glucose and lipid metabolism They increased insulin sensitivity These agents improve Hyperglycemia, hyperinsulinemia, hypertriacylglycerolemia, and improve elevated levels HbA1c

Pharmacokinetics of Thiazolidinediones They are very well absorbed after oral administration Extensively bound to serum albumin. Metabolism by cytochrome P450 isozymes. Their metabolites are excreted in the urine The parent agent eliminated via the bile. These agents not used in nursing mothers

Adverse effects of Thiazolidinediones Fluid retention, mild anemia and peripheral edema (when used in combination with insulin or insulin secretagogues) Increased risk of heart failure. Weight gain (due to fluid-retention). Hepatotoxicity with troglitazone, ,monitoring of liver function tests before initiation of therapy and during therapy Note: To date hepatotoxicity has not been associated with Rosiglitazone or Pioglitazone Increased risk of pregnancy (Reduce plasma concentrations of the estrogen-containing Contraceptives)

Contra indication of Thiazolidinediones Pregnancy Liver disease Heart failure Other uses of Thiazolidinediones Improve insulin sensitivity ,can cause ovulation in premenopausal women with polycystic ovarian syndrome

Alpha - Glucosidase Inhibitors

Acarbose Miglitol Orally active drugs Taken at the beginning of meals Hypoglycemia may Develop when used in combination with the sulfonylureas or with insulin Glucose not sucrose should be given to patients treated by alpha-glucosidase inhibitor in case of hypoglycemia (because sucrase is also inhibited by these drugs)

Mechanism of action of Acarbose and miglitol They are reversible competitive inhibitors of the intestinal α-glucosidases (enzyme responsible for hydrolysis of oligosaccharides to glucose) and reduce the postprandial digestion and absorption of starch and disaccharides Miglitol differs structurally from acarbose and is six times more potent in inhibiting sucrase.

Pharmacokinetics of Alpha - Glucosidase Inhibitors Acarbose is poorly absorbed, It is metabolized primarily by intestinal bacteria, some of the metabolites are absorbed and excreted into the urine. Miglitol is very well absorbed but has no systemic effects. It is excreted unchanged by the kidney.

Adverse effects of Alpha - Glucosidase Inhibitors flatulence, diarrhea and abdominal cramping.
Contra indication of Alpha - Glucosidase Inhibitors Patients with inflammatory bowel disease
 Colonic ulceration Intestinal obstruction.