HORMONES AND HORMONE ANTAGONISTS-I

INSULIN & DIABETES MELLITUS

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Insulin

* **Pharmacological Actions of Insulin:-** Insulin promotes the uptake and storage of glucose, proteins and fats through effects on liver, muscles, and adipose tissues. It also influences the cell growth and metabolic function of various tissues.
* **Carbohydrate metabolism:**
* a. In liver cells: it decreases glycogenolysis by inhibiting glycogen phosphorylase and increases glycogenesis by activating glycogen synthetase. It also decreases gluconeogenesis and thus conversion of non-carbohydrate substrate to glucose is inhibited.
* b. In muscles: it facilitates glucose uptake by promoting translocation of intracellular GLUT-4 onto the cell surface. It promotes glycogenesis and increases glycolysis.
* c. In Adipose tissue: it facilitates glucose uptake, it increases intracellular glucose oxidative metabolism.

Insulin

* **Protein metabolism:**
* a. In liver cells: it decreases protein breakdown and inhibits oxidation of amino acids.
* b. In muscles: it increases protein synthesis and increases amino acid uptake by muscle cells to produce a net positive nitrogen balance.
* **Fat metabolism:**
* a. In liver cells: it increases lipogenesis
* b. In adipose tissues: it increases fatty acid synthesis and TG formation; decreases lipolysis and blunts lipolytic action of adrenaline growth hormone and glucagon. Thus free fatty acid and glycerol levels remain suppressed under the influence of insulin.

Insulin- Absorption, Metabolism and Excretion:

* Insulin is administered subcutaneously. Intramuscular injections are used less often because absorption is more rapid. Being a polypeptide hormone, insulin is readily inactivated, if administered orally. In emergencies, such as severe diabetic ketoacidosis, insulin can be given intravenously. Plasma half life is less than 10 minutes. Hepatic insulinases destroy approximately 50% of circulating insulin, remainder degraded by circulating proteases. Insulin metabolism is accomplished both through actions of an insulin specific protease found in cytosol and by reductive cleavage of insulin di-sulfide bonds by glutathione–insulin transhydrogenase. In kidney, insulin that undergoes glomerular filtration is completely reabsorbed and metabolized within proximal convoluted tubules of nephron.

Insulin- Therapeutic uses:

* 1. Patients with type-1 diabetes: NPH insulin is often combined with short-acting regular insulin and is administered S.C. before meals.
* 2. Many patients with type-2 diabetes ultimately require insulin therapy.
* 3. For gestation diabetes not controlled by diet
* 4. For emergency treatment of diabetic ketoacidosis (diabetic coma): this emergency is usually faced with patients suffering with type-1 diabetes. The patients are usually dehydrated, hyperventiallating with loss of consciousness.
* 5. Non-ketonic hyperglycaemic coma: this usually occurs in elderly type-2 diabetes cases and is characterized by dehydration and haem-concentration and is usually fatal if untreated.
* 6. Short term treatment of patients with impaired glucose tolerance to overcome stress during surgery and MI.
* 7. For emergency treatment of hyperkalaemia, insulin given with glucose to lower extracellular potassium via redistribution into cells.

Insulin- Adverse Reactions:

* **Hypoglycemia:** This may result from large dose, from a mismatch between the time of peak delivery of insulin and food intake, or from superimposition of additional factors that increase sensitivity to insulin or that increase insulin-independent glucose uptake.
* **Insulin Allergy and Resistance:** Allergic manifestations are IgE-mediated local cutaneous reactions, and patients may develop life-threatening systemic responses or insulin resistance owing to IgG antibodies. Glucocorticoids have been used in patients with resistance to insulin or more severe systemic reactions.

Insulin- Adverse Reactions:

* **Lipoatrophy and Lipohypertrophy:** Atrophy of subcutaneous fat at site of insulin injection is probably a variant of an immune response to insulin, whereas enlargement of subcutaneous fat depots has been ascribed to the lipogenic action of high local concentrations of insulin.
* **Insulin Oedema:** Some degree of oedema, abdominal bloating, and blurred vision develops in many diabetic patients with severe hyperglycaemia or ketoacidosis that is brought under control with insulin. The oedema usually disappears spontaneously within several days to a week unless there is underlying cardiac or renal disease. Oedema is attributed primarily to retention of Na+.

Insulin

* **Drug Interactions:** A large number of drugs can cause hypoglycaemia or hyperglycaemia or may alter the response of diabetic patients to their existing therapeutic regimens.
* **Different preparations of insulin are:**
* a. Rapid-acting Insulin- Insulin Lispro, Insulin Aspart, Insulin Glulisine.
* b. Short-acting Insulin- Regular Novolin R, Regular Humulin R, Velosulin BR, Regular.
* c. Intermediate-acting Insulin- NPH Humulin N, NPH Novolin N.
* d. Premixed Insulin-Novolin 70/30, Humulin 70/30 and 50/50, 50/50 NPL, 5/25 NPL.
* e. Long-acting Insulin- Insulin detemir, Insulin glargine.

Insulin- Physiological role of insulin

* The biochemical actions of insulin are complex and involve many steps to integrate carbohydrate, protein, and lipid metabolism for the maintenance of fuel homeostasis. In addition to its effects on stimulating glucose uptake by tissues, insulin has five major physiological effects on fuel homeostasis. It can:
* (1) Diminish hepatic glycogenolysis by inhibiting glycogen phosphorylase.
* (2) Promote hepatic glucose storage into glycogen by stimulating glycogen synthetase.
* (3) Inhibit hepatic gluconeogenesis.
* (4) Inhibit lipolysis by inhibiting hormone-sensitive lipase activity, thereby decreasing plasma free fatty acid and glycerol levels.
* (5) Promote the active transport of amino acids into cells for incorporation into protein, thereby producing a net positive nitrogen balance.

Diabetes mellitus

* The elevated blood glucose associated with diabetes mellitus results from absent or inadequate pancreatic insulin secretion, with or without concurrent impairment of insulin action. The disease states underlying the diagnosis of diabetes mellitus are now classified into four categories:
* Type 1, insulin-dependent diabetes;
* Type 2, noninsulin-dependent diabetes;
* Type 3, and
* Type 4, gestational diabetes mellitus

Diabetes mellitus- Type 1,2:

* The hallmark of type 1 diabetes is selective B-cell destruction and severe or absolute insulin deficiency.
* Administration of insulin is essential in patients with type 1 diabetes.
* Type 2 diabetes is characterized by tissue resistance to action of insulin combined with a relative deficiency in insulin secretion. Individual have more resistance or more B-cell deficiency, and abnormalities may be mild or severe. Although insulin is produced by B cells in these patients, it is inadequate to overcome the resistance, and blood glucose rises. The impaired insulin action also affects fat metabolism, resulting in increased free fatty acid flux and triglyceride levels and reciprocally low levels of high-density lipoprotein.
* Individuals with type 2 diabetes may not require insulin to survive, but benefited from insulin therapy to control the blood glucose.

Diabetes mellitus-Type 3,4:

* Type 3 Diabetes Mellitus-refers to multiple other specific causes of elevated blood glucose: non-pancreatic diseases, drug therapy, etc.
* Type 4 Diabetes Mellitus Gestational diabetes (GDM)- is defined as any abnormality in glucose levels noted for the first time during pregnancy. During pregnancy, the placenta and placental hormones create an insulin resistance that is most pronounced in the last trimester. High-risk women should be screened immediately. Screening may be deferred in lower-risk women until 24th to 28th week of gestation.

Diabetes mellitus-Rapid-Acting Insulin

* i. Insulin lispro: is produced by recombinant technology. To enhance the shelf-life of Insulin in vials, when injected subcutaneously, the drug quickly dissociates into monomers and is rapidly absorbed with onset of action within 5–15 minutes and peak activity as early as 1 hour.
* ii. Insulin aspart: Its absorption and activity profile is similar to that of Insulin lispro, and it is more reproducible than regular Insulin, but has similar binding properties, activity, and mitogenicity characteristics to regular Insulin and equivalent immunogenicity also.

Diabetes mellitus-Rapid-Acting Insulin

* iii. Insulin glulisine: Its absorption, action, and immunologic characteristics are similar to the other injected rapid-acting Insulin. After high-dose Insulin glulisine- Insulin receptor interaction, there may be downstream differences in IRS-2 pathway activation relative to human Insulin.
* iv. Inhaled human Insulin is a powder form of rDNA human Insulin administered through an inhaler device for pre-prandial and blood sugar correction use in adults with type 1 and 2 diabetes. Because of concerns about lung safety, it is not used in children, teenagers, or adults with asthma, bronchitis, emphysema, smokers. This route of administration is well tolerated; users achieve target blood glucoses after 6 months of therapy with inhaled human Insulin.

Diabetes mellitus- Intermediate and Long-Acting Insulin

* c. Intermediate-Acting and Long-Acting Insulin:
* i. NPH (NEUTRAL PROTAMINE HAGEDORN, OR ISOPHANE) Insulin-It is intermediate-acting Insulin wherein absorption and onset of action are delayed by combining appropriate amounts of Insulin and protamine, so that neither is present in an uncomplexed form. After subcutaneous injection, proteolytic tissue enzymes degrade the protamine to permit absorption of Insulin. Onset of action is 2–5 hours and duration of 4–12 hours; and given two to four times daily for Insulin replacement in patients with type 1 diabetes.
* ii. Insulin GLARGINE-is a soluble, ultra-long-acting Insulin analogue. Has a slow onset of action (1–1.5 hours) and achieves a maximum effect after 4–6 hours. This maximum activity is maintained for 11–24 hours or longer.

Diabetes mellitus- Intermediate and Long-Acting Insulin

* iii. Insulin DETEMIR- has the most reproducible effect of intermediate- and long-acting Insulin, and its use is associated with less hypoglycaemia than NPH Insulin. Onset of action of 1–2 hours and duration of action of more than 24 hours.
* iv. Mixtures of Insulin-Because intermediate-acting NPH Insulin require several hours to reach adequate therapeutic levels, their use in type 1 diabetic patients requires supplements of rapid- or short-acting Insulin before meals. These are often mixed together in the same syringe before injection. Insulin lispro, aspart, and glulisine can be acutely mixed (ie, just before injection) with NPH Insulin without affecting their rapid absorption.

Diabetes mellitus- Oral hypoglycaemic drugs

* Oral hypoglycaemic drugs Classification:-
* 1. Insulin secretogogues:
* a. sulphonylureas ex: tolbutamide, gliburide, glipizide, glimepride, gliclazide
* b. Meglitine analogues Ex: Ropglimide, Nateglinide
* 2. Insulin sensitizers:
* a. Biguanides Ex: Metformin, phenformin.
* b. Thiazolidine diones ex: roliglitazone, proglitazones.
* 3. Alpha-glucosidase inhibitors: Ex:- acarbose, miglitol.

Diabetes mellitus- Oral hypoglycaemic drugs

* Pharmacology of sulfonyl ureas:-
* First-Generation Sulfonylureas: Ex-Tolbutamide, Chlorpropamide, Tolazamide.
* Second-Generation Sulfonylureas: Ex-Glyburide, Glipizide, Glimepiride.
* Mechanism of Action:-The major action of sulfonylureas is to increase insulin release from the pancreas. Two additional mechanisms of action have been proposed—a reduction of serum glucagon levels and closure of potassium channels in extra-pancreatic tissues. The latter is of unknown clinical significance.

Diabetes mellitus- Oral hypoglycaemic drugs

* First-Generation Sulfonylureas are not frequently used in management of diabetes mellitus because of their relatively low specificity of action, delay in time of onset, occasional long duration of action, and variety of side effects. They are occasionally used in patients who have achieved previous adequate control with these agents.
* a. Acetohexamide shows uricosuric activity, an action that may be of benefit in diabetic patients who also have gout.
* b. Chlorpropamide has a relatively slow onset of action, with its maximal hypoglycaemic potential often not reached for 1 or 2 weeks. Several weeks may be required to eliminate the drug after discontinuation of therapy. It can cause flushing, particularly when taken with alcohol, and can also cause hyponatremia. This effect has been employed to treat some patients who have partial central diabetes insipidus, an unrelated condition due to a pituitary ADH deficiency.

Diabetes mellitus- Oral hypoglycaemic drugs

* c. Tolazamide is an orally effective hypoglycemic drug that causes less water retention.
* d. Tolbutamide is a relatively short-acting compound that may be useful in patients who are prone to hypoglycaemia.
* Second-Generation Sulfonylureas display higher specificity and affinity for sulfonylurea receptor and more predictable pharmacokinetics. It may also exert mild diuretic effects on kidney and are highly protein bound, primarily through non-ionic binding.
* a. Glyburide, also known as glibenclamide, is approximately 150 times as potent as tolbutamide on a molar basis and twice as potent as glipizide. It is completely metabolized in liver to two weakly active metabolites before excretion in urine. Its average duration of action is 24 hours.

Diabetes mellitus- Oral hypoglycaemic drugs

* b. Glipizide is similar to glyburide, but it is metabolized by the liver to two inactive metabolites; these metabolites and glipizide are excreted through urine.
* c. Glimepiride is metabolized to at least one active metabolite. It is quickly absorbed from gastrointestinal tract within an hour of oral administration and excreted in urine and faeces. Its half-life varies from 5 to 9 hours depending on frequency of multiple dosing.
* **Absorption, Metabolism, and Excretion:**
* Readily absorbed from gastrointestinal tract following oral administration but undergo varying degrees and rates of metabolism in the liver and/or kidney; the biological half-lives vary greatly, Sulfonylureas and their metabolites are excreted either urine or in faeces.

Diabetes mellitus- Oral hypoglycaemic drugs

* Clinical Uses: Sulfonylureas are effective in individuals with mild to moderate type II diabetes. The chance for successful glycemic control with sulfonylureas is poor in diabetic patients requiring more than 40 units of insulin per day.
* Adverse Effects:
* a. Hypoglycaemia, provoked by inadequate calorie intake (e.g., skipping a meal), or increased caloric needs (e.g., increased physical activity).
* b. Sulfonylureas also tend to cause weight gain; some of this weight can be due to fluid retention and oedema.
* c. Less common adverse reactions include muscular weakness, ataxia, dizziness, mental confusion, skin rash, photosensitivity, blood dyscrasias, and cholestatic jaundice.

Diabetes mellitus- Oral hypoglycaemic drugs

* Drug Interactions:

* A decrease in alcohol tolerance is seen. Sulfonylureas are highly bound to plasma proteins and metabolized by microsomal enzymes, co-administration of drugs capable of displacing them from their protein binding sites or inhibiting their metabolism also may potentiate hypoglycaemia.

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