# "Antidiabetic Drugs"

Diabetes mellitus type 1 is due to insulin deficiency. Treatment is dietary modification plus insulin administration.

Diabetes mellitus type 2 is due to reduced secretion of insulin or insulin resistance (lack of sensetivity of target organs to insulin).Treatment is dietary modification with or without oral hypoglycemic agents and/or insulin.

## *INSULIN*

**Actions and effects**:

It binds with and activates receptors on the cell membranes of most body cells. Target tissues are liver, muscle and adipose tissue. After insulin-receptors binding occurs cell membranes become highly permeable and allow entry of glucose, amino acids, fatty acids and potassium. This results in the following effects:

1- reduction in blood glucose due to:

a) increased glucose uptake in peripheral tissues (which oxidize glucose or convert it to glycogen or fat)

b) decreased hepatic output of glucose by reducing glycogenolysis and gluconeogenesis .

2-anabolic effects :

- in muscles and most other cells insulin facilitates amino acid uptake and their synthesis into proteins, as well as inhibits proteins breakdown so decreased amino acids output ( precursors for hepatic gluconeogenesis).
-In adipose tissue insulin inhibits lipolysis and favors triglyceride synthesis.

3 -supression of ketogenesis ( ketone body synthesis) by: a) Inhibiting lipolysis, in adipose tissues, and release of free fatty acids; the major source for hepatic ketogenesis. b) Suppressing hepatic oxidation of free fatty acids to ketone bodies.

4-stimulation of $K^+$ entry into cells, by stimulating $Na^+/K^+$ ATPas action.

**Sources of commercial insulin preparations**:

- pork or beef pancreas.
- human insulins: made either by enzymatic modification of porcine insulin or by using recombinant DNA technology e.x. soluble insulin
-human insulin analogues :made by modifying the amino acid sequence of the human insulin molecule to produce insulin preparations with different onset and durations of action but similar pharmacodynamic effects e.x. insulin lispro and insulin glargin.

**Pharmacokinetics**: Insulin cannot be taken orally because; it is a peptide and digested in GIT.

Main route of administration: subcutaneous but can be given IV and IM .

It is cleared out of circulation rapidly because of binding to peripheral tissues and metabolism in the liver, kidneys, muscels, and plasma and excreted by kidneys. The plasma t1/2 is 5-9 min.

**Factors affect subcutaneous absorption:**

- Site: The abdomen has the fastest rate of absorption, followed by the arms, thighs, and buttocks.
- Massage of injection site, exercise and heat application increases absorption, probably by increasing blood flow to the skin.
- Areas of lipohypertrophy usually show slower absorption rate.

**Dose and Daily insulin requirement in diabetics:**

Daily pancreatic secretion is 30-40-units, and most insulin- deficient diabetics need 30-50 units insulin per day. The standard strength (amount) of insulin in vials is 100 units/ml.

**insulin preparations** :

1) *Short- acting:* ex. **soluble insulin**:
   - clear solution
   - onset of action is (30min after subcutaneous injection so, need to be injected 30minutes before the main meals to control the early postprandial hyperglycaemia.
   - Duration of action is (8 hrs) requires frequent administration.
   - **Can be given i.v.: acts faster and can be given in high dose** for **treatment** of :
     a) ketoacidosis : Keton bodies inhibit glucose uptake by brain and muscle
     b) acute short term Insulin resistance ( Insulin requirement increases > 200 U/day) due to infection, trauma, surgery, emotional stress; where corticosteroids and other hormones are produced in excess as a reaction to the stress and oppose insulin actions.
     c) hyperkalaemia

2) *Rapid -acting insulins*: ex. **insulin lispro**
   - *Clear solution* of modified human insulin

- onset of action: very rapid ( within 15 minutes) after subcutaneous injection; can be injected immediately before or even after the meal to control postprandial hyperglycaemia.
- duration of action is 5 hours. This decreases the risk of late post meal hypoglycaemia.

3) Intermediate acting insulins: e.x. **NPH** (Neutral protamine Hagedorn) (isophane insulin)

- Cloudy neutral suspension of insulin with equivalent amount of Protamine, a basic protein that delays absorption and prolongs the duration of action of insulin.
- onset of action is 1.5 hours and duration of action is 12 hours.

4) Long acting insulins: e.x. **insulin glargine**

- -clear solution, has an acidic pH . When administered subcutaneously, insulin precipitates at the neutral pH in tissues at injection site then dissociates slowly to enter the circulation. onset of action is delayed (1.5) hrs so, it does not control postprandial hyperglycaemia, but relatively a low peakless continuous blood levels of insulin are maintained for up to 24 hours. Thus it is suitable for once daily administration..
- should not be mixed with other forms of insulin in same syringe to avoid disturbance of its pH and lose of efficacy.

5) Biphasic insulins: a premixed comination of fast and long- or intermediate - acting insulins ex. insulin mixtard that contain 30% soluble insulin plus 70% NPH insulin.

**Side *effects*:**

*1*-Hypoglycemia- If it is not treated it may progress to coma.

2- Lipodystrophy (*hypertrophy* or *atrophy*) of subcutaneous fatty tissues at injection site; can be prevented by advising the patient to change sites within the injection area.

3-allergy as urticaria and anaphylaxis due to immune reactions to animal insulin preparations or additive proteins. Bovine insulin is more antigenic than porcine insulin.

4-Local reactions as swelling and erythema.

5-Insulin resistance due to antibodies against animal insulins or additive proteins. Insulin requirement may increase > 200 U/day. Switching to human insulins can reduce resistance.

# "Oral Antidiabetic Drugs"

- Only effective for type 2 diabetes
- require presence of endogenous insulin for their actions so; ineffective in type 1 diabetes .
- Ineffective during pregnancy- should be replaced by insulin
- Ineffective and should be temporarily replaced by insulin in acute conditions where insulin requirement is increased rapidly i.e diabetic ketoacidosis and acute stress conditions as during surgeries, acute infections and myocardial infarction.

***Classification:***

**(1) Drugs that increase insulin secretion:**

a) **Sulphonylureas:**

are Sulphonamide derivatives

are taken orally before the main meals.

are preferred in lean or ideal weight patients because they cause weight gain.

promote insulin release …

can cause hypoglycaemia in diabetic as well as in non- diabetic person.

Mechanism of action: They stimulate release of insulin from pancreas. They act on pancreatic β cell membrane-- block the ATP-sensitive $K^+$ channels; this prevent $K^+$ exit which results in depolarization. This enhances $Ca^{+2}$ entry; and the rise in intracellular $Ca^{+2}$ enhances the rate of insulin secretion in response to rise in blood glucose level.

-After chronic administration they sensitize the target tissues ( liver, muscle and adipose tissue) to the action of insulin by increasing the number of insulin receptors.

Classification:

1st generation agents ex. chloropropamide (withdrawn due to side effects) , Tolbutamide

2ndgeneration agents have similar efficacy but they are more potent than 1st generation agents ex. glibenclamide, glipizide, glimepiride :

- Selection does not depend on potency but it depends on duration of action, side effects as well as patient's age, renal function and liability to develop hypoglycaemia.
- Long acting members as glibenclamide (glyburide) and glimepiride can be given once daily as well as they cause more incidence of late post meal hypoglycemia, so they are not preferred in elderly.

- Tolbutamide, gliclazide and glipizide have shorter duration of action…less risk of prolonged hypoglycaemia……more suitable in elderly.
- Glibenclamide is excreted by liver and kidney…… dose needs to be adjusted in patient with liver or renal impairment.
- gliclazide ,glipizide and tolbutamide: are metabolized in liver to inactive metabolites before excretion by kidney ….safe in patient with impaired renal function.

Side effects:

- Hypoglycemia.
- Weight gain because insulin release stimulates appetite.
- Secondary failure after months or years due to declining of beta cells function and insulin resistance.
- Teratogenic in animals… avoid during pregnancy

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**b)Meglitinides** ex. repaglinide, nateglinide

- Stimulate insulin release by a similar mechanism as sulphonylureas.
- Induce rapid very "short- lasting" insulin release. It is administered before each major meal to boost the postprandial insulin release and control postprandial hyperglycaemia.
- Because of short lasting action so lower risk of hypoglycemia.
- metabolized in liver –should be avoided in liver impairment .

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**c)Incretin analogues** ex. exenatide

Mechanism : an analogue of the endogenous glucagon-like-peptide 1 ( incretin) that is secreted from upper small intestine in response to glucose and enhances postprandial insulin secretion, suppresses glucagon secretion, slows gastric emptying and decreases appetite).

used in overweight patients given Sc Side effects: nausea

**d)sitagliptin**:, inhibits dipeptidyl peptidase-4 enzyme that is responsible for breakdown of GLP-1 and potentiate its action. It is administered orally**.**

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**(2) Insulin sensetizers (increase the sensitivity of target organs to insulin)**

a)**Biguanides**: **ex.** *Metformin*

Mechanism of action: It prevents hyperglycaemia as it

1- Suppresses hepatic gluconeogenesis and glucose output.

2-sensetizes the target tissues (especially muscle) to the action of insulin so, enhances glucose utilization.

3-reduces intestinal absorption of glucose.

- ❖ Can be given after main meals
- ❖ does not cause hypoglycemia because it does not promote insulin release
- ❖ is excreted unchanged by kidneys…may accumulate to toxic levels in renal impairment.
- ❖ does not cause weight gain so, it is preferred for those overweight and obese patients having normal renal function.
- ❖ Other uses : treatment of polycystic ovary syndrome (a condition of insulin resistance that contributes to hyperandrogenism,hisutism,menstrual disorders and infertility).

Side effects:

- *diarrhea*, anorexia , *nausea* and metallic taste
- ❖ lactic acidosis in patients with renal impairment or liver failure.
- Vitamin B12 deficiency ( due to impaired absorption). Patient may need vitamin B12 injections periodically.

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b)**Thiazolidinediones** (glitazones):
e.x. pioglitazone
*Mechanism of action:* sensitizes the peripheral tissues (especially fatty tissues) to the action of insulin by activation of certain genes.
-do not promote insulin release…..do not cause hypoglycemia.

- ❖ *Side effects*: fluid retention, peripheral oedema , weight gain .

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(3) **Alpha glucosidase inhibitors**: e.x.. **acarbose**
Mechanism of action:
inhibits α- glucosidase enzymes, responsible for digestion of complex carbohydrate in small intestine, so prevents the postprandial rise in blood glucose.

- ❖ does not cause hypoglycemia.
- ❖ is taken just before main meals.
- ❖ Side effects: flatulence, diarrhea, abdominal pain and distension

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**Hypoglycaemia**

Precipitating factors: missing a meal, unusual physical exercise, over dose of insulin or oral hypoglycaemic drugs and co-administration of drugs that intensify hypoglycaemia as salicylates, sulphonamides and cimetidin .
Warning signs: sweating, tremor, tachycardia and palpitation (Which drugs masking these symptoms and why?
Treatment:

- ➢ glucose must be given orally or i.v.( if the patient is unconscious)

- glucagon S.C. or I.M enhances glycogenolysis and increases hepatic glucose output, but in about 45 minutes from onset of coma the hepatic glycogen will be exhausted and glucagon will be useless.