Hypoglycemic drugs

**Mechanism of action**

1. Increases insulin sensitivity "insulin sensitisers" because it lowers insulin levels.  
2. It reduces the rate of glucose necrosis, and hence hepatic glucose output.  
3. It has an effect on gut glucose uptake and utilisation.  
4. At the molecular level, metformin acts as a weak inhibitor of mitochondrial respiration, which activates AMPK (AMP) and mTOR (ATP). This has:
   - a Direct effect on flux through glucose utilisation.  
   - It activates intracellular energy sensor AMPK-kine, which is involved in:
     - GLUT4 metabolism and  
     - Fat and fatty acid oxidation,  
   - BUT its mechanism of action remains unclear at a cellular level.  

**It does not:**

1. Affect insulin secretion,  
2. Induce hypoglycaemia  
3. Predispose to weight gain.  

N.B., has established benefits in microvascular disease.

**Use:**

- It is employed as first-line therapy in all patients who tolerate it, and  
- Its use is maintained when additional agents are added as glycaemia deteriorates.

**Dose:**

- Introduced at low dose (500 mg twice daily) to minimise risk of GIT side effects.  
- The usual maintenance dose is 1 g twice daily.

**Side effects:**

- GIT side effects with metformin:
  - diarrhoea,  
  - abdominal cramps,  
  - bloating,  
  - nausea.

- Lactic acidosis in parenchymal, hepatic impairment, alcohol excess:
  - Dose halved if GFR 30-45 ml/min  
  - Shouldn’t used if GFR < 30 ml/min, hepatic impairment, alcohol excess.

**Metformin:**  
- It’s the only biguanide now available.  
- It is now widely used as first-line therapy for type 2 diabetes, irrespective of body weight.  
- It given adjunct to insulin therapy in obese patients with type 2 diabetes.

**Biguanides**

**Metformin:**

- Their action is to bind to the sulphonylurea receptor on the cell membrane,  
- which closes ATP-sensitive potassium channels and blocks potassium efflux resulting in depolarization which promotes influx of calcium, a signal for insulin release.  
- They are ineffective in patients without a functional beta-cell mass & their effect wears off with the beta-cell mass declines.

**It does cause:**

1. Hasten beta-cell apoptosis.  
2. Induce hypoglycaemia.  
3. Promote weight gain.  

N.B., has established benefits in microvascular disease.

**Use:**

- Often used as an add-on to metformin, if glycaemia is inadequately controlled on metformin alone (see Fig. above).  
- The dose-response of all sulphonylureas is steepest at low doses.

**Side effects:**

- Weight gain – not preferred to be used in obese individuals.  
- Hypoglycaemia  
- Hypoglycaemia occurs because the closure of KATP channels brings about unregulated insulin secretion, even with normal or low blood glucose levels.  
- Sulphonylureas should be used with care in patients with liver disease.  
- Patients with renal impairment should only be given those primarily excreted by liver.

**Sulphonylureas**

**Thiazolidinediones ‘glitazones’ or PPARγ agonists**

- They reduce insulin resistance by bind and activate peroxisome proliferator-activated receptor (PPARγ), a nuclear receptor present mainly in adipose tissue that regulates the expression of several genes involved in metabolism.  
- TZDs potentiate the effect of endogenous or injected insulin:  
  - Directly (in the adipose cell)  
  - Indirectly (by altering release of "adipokine", such as adiponectin, which alter insulin sensitivity in the liver).  
- Act indirectly via the glucose–fatty acid cycle, lowering free fatty acid levels and thus promoting glucose consumption by muscle.  
- Reduces hepatic glucose production, (effect that is synergistic with that of metformin)

**It doesn’t & Does cause:**

1. Hypoglycaemia does not occur (Plasma insulin concentrations are not increased)  
2. TZDs increase pre-adipocyte differentiation, resulting in an increase in fat mass and in body weight.

The "incretin effect" is:

- The augmentation of insulin secretion seen when a glucose stimulus is given orally rather than IV, and reflects the release of incretin peptides from the L cells in intestine:
  - 1- Glucagon-like peptide 1 (GLP-1)  
  - 2- Gastric inhibitory polypeptide (GIP).  
  - DPP-4 (dipeptidyl peptidase 4) rapidly inactivates GLP-1.

**Use:**

- A number of adverse effects become apparent and their use has declined.  
- First-line therapy (Metformin and Sulphonylureas )

**Side effects:**

1. - Rosiglitazone:  
   - Increase the risk of MI (withdrawn in 2010).  
2. - Pioglitazone:  
   - More effective in insulin-resistant patients.  
   - Has a beneficial effect in reducing fatty liver and NASH  
   - Usually added to metformin with or without sulphonylurea therapy may be given with insulin therapy.

**Incretin-based therapies:**

**- GLP-1 analogues**

**- DPP-4 inhibitors**

**Incretin-based therapies:**

- GLP-1 analogues  
- DPP-4 inhibitors

**Doesn’t cause hypoglycaemia:**

Unlike sulphonylureas, they only  
- promote insulin secretion when there is a glucose "trigger" for insulin secretion.

**Inclusion-based therapy:**

1. - "glitizones", or DPP-4 inhibitors:
   - Prevent breakdown  
   - Enhance concentrations of endogenous GLP-1 & GIP.  
   - Drugs: 1- Lixagliptin  
   - 2- Vildagliptin  
   - 3- Saxagliptin  
   - 4- Linagliptin.

2. - GLP-1 receptor agonists:
   - have a similar structure to GLP-1 but have been modified to resist breakdown by DPP-4.  
   - These agents are not orally active and have to be given by subcutaneous injection.  
   - They have a key advantage over the DPP-4 inhibitors: because the GLP-1 activity achieved is supra-physiological:  
     - it delays gastric emptying and  
     - as the level of the hypothalamus, decreases appetite.  
   - Thus, injectable GLP-1 analogues lower glucose blood and result in weight loss – an appealing therapy, as the majority of patients with type 2 diabetes are obese.

**- Drugs:**

1. - Exenatide (once daily)  
   - Lixagliptide (once daily).

**SGLT2 inhibitors**

**α-glucosidase inhibitors**

- a-glucosidase inhibitors (Acarbose) taken with each meal) competitively inhibits alpha-glucosidase enzymes situated in the brush border of the intestine,  
- Reducing absorption of dietary carbohydrate  
- So, undigested starch then enter the large intestine where it will be broken down by fermentation causing (S.E.):  
  - Abdominal discomfort  
  - Flatulence  
  - Diarrhoea can result.