Diabetes Mellitus Masterclass
Chapter 4

STARTING TREATMENT

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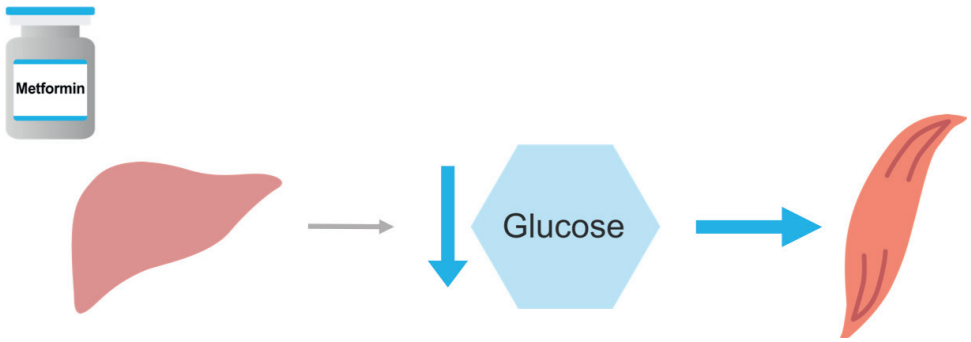
METFORMIN

Several oral medications are available for use in treating diabetes.

First line therapy for patients with type 2 diabetes is metformin.

Mechanism of action

Its mechanism of action is unclear, but it acts to lower hepatic glucose production, and also helps increase peripheral glucose uptake, likely through improved insulin sensitivity.



Benefits

- 1–2% A1c lowering
- Generally well tolerated
- Can help to prevent cardiovascular disease

Dosing

- Start at 500 mg once daily
- Increase by 500 mg every week to maximum tolerated dose of 1000 mg twice daily

Side effects

- Diarrhea, bloating, and gas (25%)
- Vitamin B12 deficiency (10%)

Contraindications

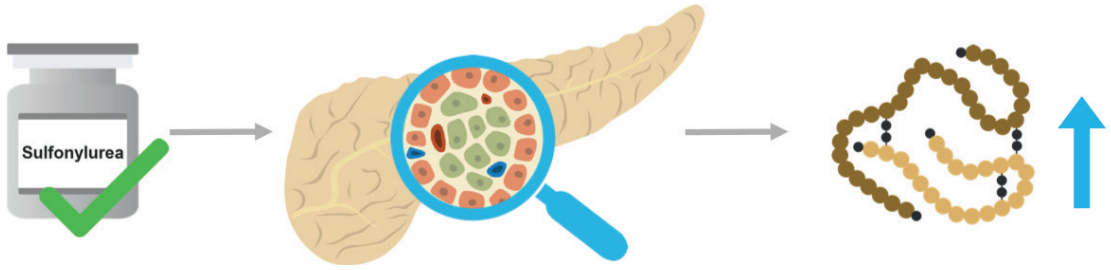
- Significant renal dysfunction
  - Glomerular filtration rates (GFR) is over 60: no contraindications to using metformin
  - GFR is 45–60: no dose adjustment needed, monitor creatinine every three months
  - GFR is 30–45: do not start metformin, decrease maximum dose to 1000 mg daily for those already on it
  - GFR is < 30: discontinue metformin

SULFONYLUREAS

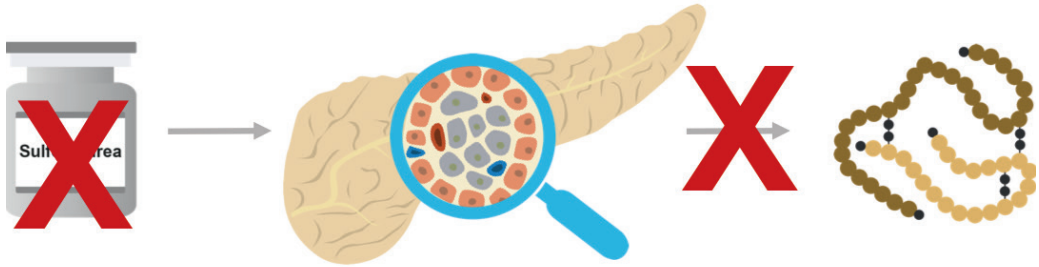
Sulfonylureas are a commonly used second-line agent for treatment of type 2 diabetes. They are often used in combination with metformin.

Mechanism of action

Sulfonylureas help regulate blood sugar levels by stimulating insulin release from the pancreas. This requires functioning beta cells so sulfonylureas are only used for type 2 diabetes.



Type 2



Type 1

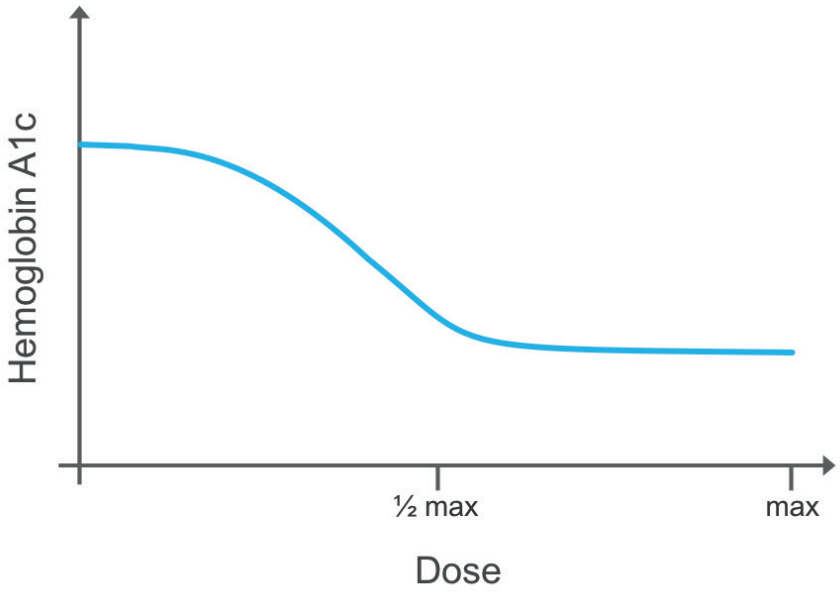
Benefits

- 1% A1c lowering when added to metformin
- Well tolerated with minimal side effects
- Low cost

Dosing

- Glimepiride: 1 mg–8 mg daily
- Glyburide: 2.5 mg–10 mg daily
- Gliclazide: 40–240 mg daily (not available in the US)
- Glipizide: 2.5 mg–10 mg twice daily

Maximal glycemic effect is usually achieved at half maximal dose



Side effects

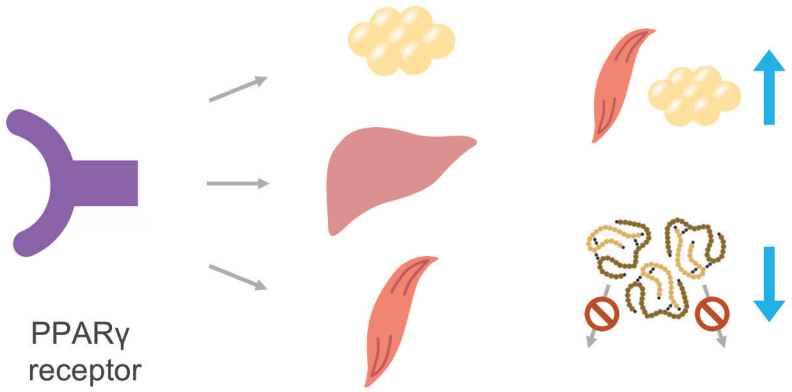
- Increased risk of hypoglycemia (due to increased insulin production)
- Weight gain

THIAZOLIDINEDIONES (TZDs)

TZDs are most often combined with other drugs, such as metformin, and are rarely used as monotherapy.

Mechanism of action

TZDs act to improve insulin sensitivity through activation of the PPAR gamma receptors. This leads to alterations in gene transcriptions and changes in protein expression in adipose tissue, liver, and skeletal muscle. This ultimately results in increased glucose utilization and decreased insulin resistance.



Benefits

- 1–1.5% A1c lowering when added to metformin
- No risk of hypoglycemia
- Durable effect (only 15% failure at 5 years)

Dosing

- Pioglitazone: start at 15 mg daily (can be increased to 45 mg daily)
- Dose changes can take several weeks to have full effect
- Side effects are dose dependent (use lowest effective dose)

Side effects

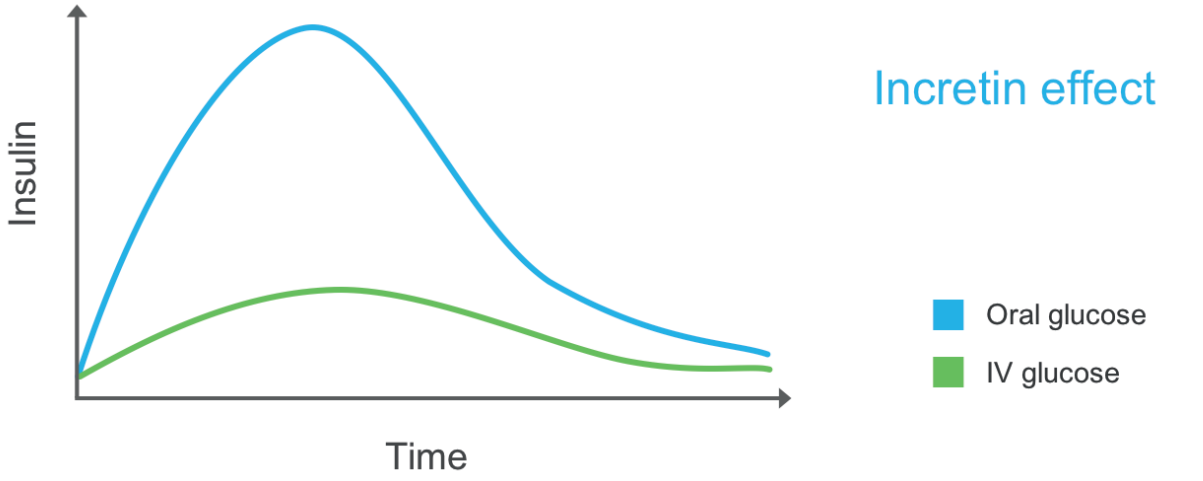
- Fluid retention
- Weight gain
- Osteoporosis
- Possible risk of bladder cancer

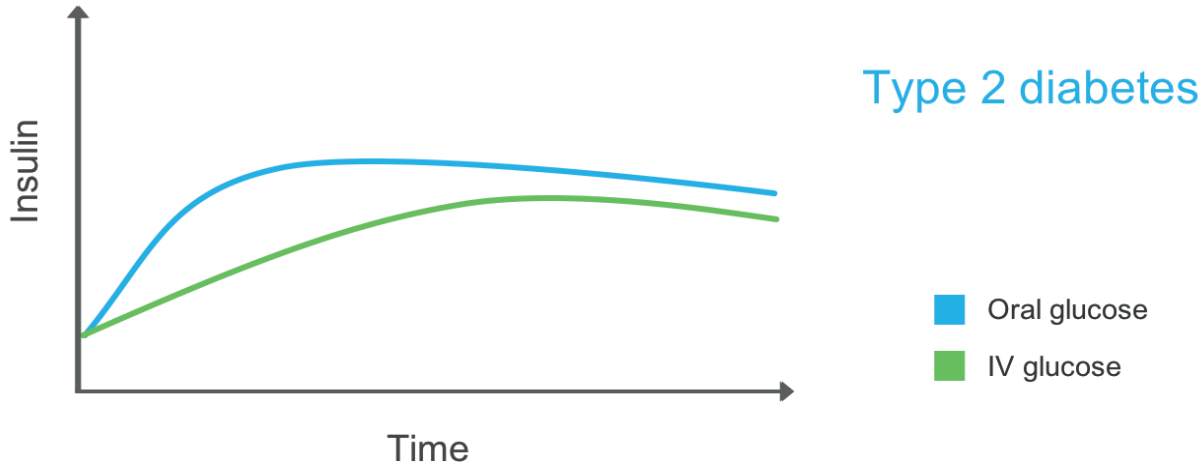
Contraindications

- History of congestive heart failure (CHF)—due to increased fluid retention and risk of CHF exacerbation
- History of bladder cancer

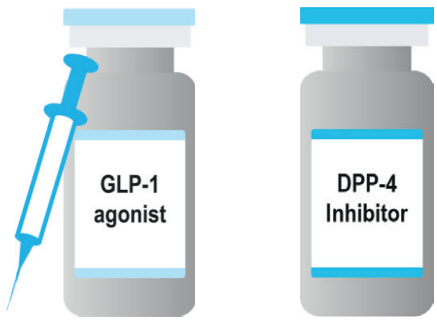
INCRETINS

One of the newer classes of diabetes medications is the incretins, which are related to hormones secreted from the gastrointestinal system that stimulate insulin release in response to food intake. These hormones are responsible for what is known as the **incretin effect**, where oral glucose causes a greater increase in insulin levels compared to the same amount of glucose given intravenously (IV). This effect is blunted in type 2 diabetes.

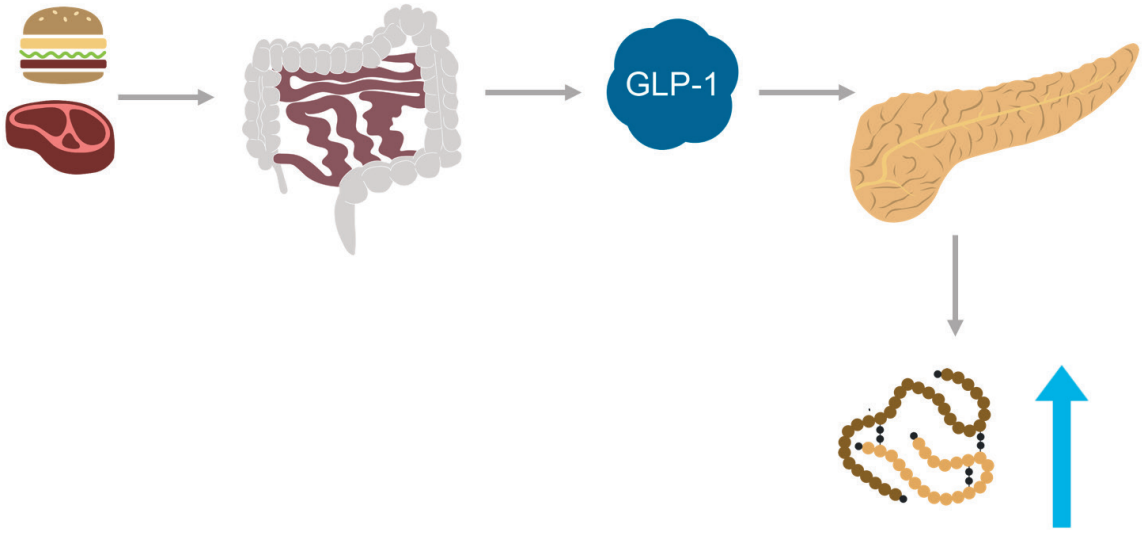




This group includes two classes of medications. GLP-1 agonists are administered as an injection, while DPP-4 inhibitors are taken orally.



GLP-1 is a hormone released by the L-cells of the small intestine in response to a meal. GLP-1 then travels



to the pancreas, where it enhances insulin release. Normally, GLP-1 is rapidly degraded by a dipeptidyl peptidase-4 (DPP-4). This limits its activity.

GLP-1 receptor agonists

Mechanism of action

These synthetic GLP-1 agonists bind and trigger signaling via the GLP-1 receptor, but are resistant to DPP-4 degradation, so they increase GLP-1 signaling to supraphysiologic levels. They also delay gastric emptying, which slows the post-meal rise in glucose and increases satiety.

Benefits

- Low risk of hypoglycemia
- May cause weight loss
- 1.0–1.5% A1c lowering

Dosing

- Exenatide: 5–10 mcg twice daily or 2 mg once weekly
- Lixisenatide: 10–20 mcg once daily
- Liraglutide: 1.2–1.8 mg once daily
- Dulaglutide: 0.75–1.5 mg once weekly
- Semaglutide: 0.5–1.0 mg weekly

Side effects

- Nausea (less common with once weekly formulations)

Contraindications

- History of pancreatitis or pancreatic cancer
- History of medullary thyroid cancer (increase in MTC seen in preclinical rodent studies)
- Some require dose adjustment with renal dysfunction
- Gastroparesis

DPP-4 inhibitors

Mechanism of action

Inhibition of DPP-4 prevents the breakdown of GLP-1, and prolongs the activity of endogenous GLP-1. Unlike GLP-1 receptor agonists, DPP-4 inhibitors have limited effects on gastric emptying and satiety.

Benefits

- Low risk of hypoglycemia
- Weight neutral
- 0.5–1.0% A1c lowering

Dosing

- Sitagliptin: 100 mg daily
- Saxagliptin: 5 mg daily
- Vildagliptin: 50 mg twice daily (not available in the US)
- Linagliptin: 5 mg once daily
- Alogliptin: 25 mg once daily

Side effects

- No significant side effects

Contraindications

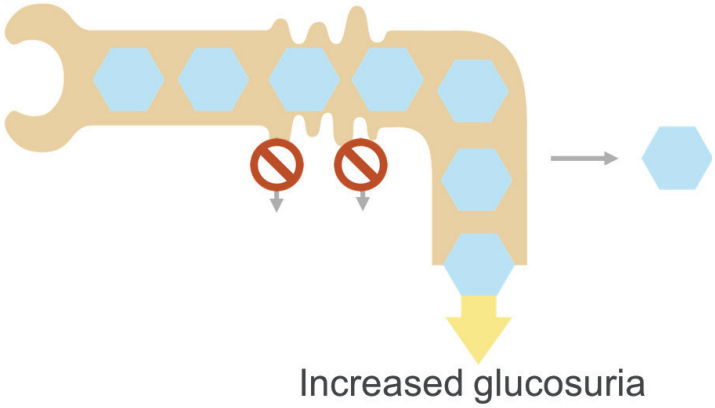
- Dose adjustment needed in renal dysfunction (except with linagliptin)

SGLT-2 INHIBITORS

SGLT-2 are effective as monotherapy and in combination with other medications.

Mechanism of action

The SGLT-2 inhibitors block the reuptake of glucose in the renal tubules, and cause glycosuria at much lower levels of glucose. This results in lower blood sugars, via increased renal glucose losses.



Benefits

- ~1% A1c lowering in nearly all cases
- Low risk of hypoglycemia
- May result in weight loss

The SGLT-2 inhibitors do appear to provide cardiovascular protection, particularly for high-risk patients, with lower rates of death related to cardiovascular disease, hospitalization for congestive heart failure, and all causes of mortality in patients taking these medications.

Dosing

- Canagliflozin: 100–300 mg daily
- Dapagliflozin: 10 mg daily
- Empagliflozin: 10–25 mg daily
- Ertugliflozin: 5–15 mg daily

Side effects

- Polyuria
- Vaginal yeast infections
- Balanitis
- Urinary tract infections
- Orthostatic hypotension (due to volume depletion)

Contraindications

- Renal dysfunction

READING LIST

A review of medications for treatment of type 2 diabetes

Wright, JJ and Tylee, TS. 2016. Pharmacologic Therapy of Type 2 Diabetes. *Med Clin North Am.* **100**: 647–663. https://www.ncbi.nlm.nih.gov/pubmed/27235609

The controversy surrounding TZDs

Home, PD, Pocock, SJ, Beck-Nielsen, H, et al. 2009. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet.* **373**: 2125–2135. https://www.ncbi.nlm.nih.gov/pubmed/19501900

Mannucci, E, Monami, M, Lamanna, C, et al. 2008. Pioglitazone and cardiovascular risk. A comprehensive meta-analysis of randomized clinical trials. *Diabetes Obes Metab.* **10**: 1221–1238. https://www.ncbi.nlm.nih.gov/pubmed/18505403

Nissen, SE and Wolski, KN. 2007. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med.* **357**: 100. https://www.ncbi.nlm.nih.gov/pubmed/17517853