Glucose lowering agents

Goals of therapy

- To eliminate symptoms related to hyperglycemia
- To reduce or eliminate the long-term microvascular and macrovascular complications of DM
- To achieve as normal a lifestyle as possible

Index	Goal
Glycemic control	
Heamoglobin A1C	<7.0%
Preprandial capillary plasma glucose	3.9–7.2 mmol/L
Peak postprandial capillary plasma glucose	<10.0 mmol/L

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- The glycemic goal
  - The haemoglobin A_{1C} (Hb A_{1C}) as close to normal as possible without significant hypoglycemia
  - The target Hb A_{1C} should be <7%
  - A higher Hb A_{1C} goal for the very young or old or comorbid conditions
  - Depends on the frequency and severity of hypoglycemia
  - A_{1C} of 6% or less is not recommended

- **Should not be used for glucose management of severely ill individuals**
- **Are ineffective in type 1 DM except**
  - **alpha glucosidase inhibitors**

- **mild to moderate hyperglycemia**
  - **FPG < 11.1–13.9 mmol/L**
  - **single, oral glucose-lowering agent**
  - **Usually metformin or sulfonylurea (have been used for many years)**
  - **Metformin is the preferred agent**

- **severe hyperglycemia**
  - **FPG > 13.9 mmol/L**
  - **A stepwise approach**
  - **Start with a single agent then add a second agent to achieve the glycemic target**
  - **Insulin can be used as initial therapy in individuals**
    - **Results in more rapid glycemic control**

- For overweight and obese patients with type 2 diabetes
  - 5% weight loss is needed to achieve beneficial outcomes in glycemic control, lipids, and BP

- When choosing glucose-lowering medications for patients with type 2 diabetes and overweight or obesity, consider the medication's effect on weight

- Type 2 diabetes who have established atherosclerotic CVD (ASCVD) or indicators of high risk, established kidney disease, or HF add antidiabetic agents with CVD benefits

For ASCVD,HFetc

- A sodium–glucose cotransporter 2 (SGLT2) inhibitor
  - Empagliflozin, canagliflozin, dapagliflozin
- or
- glucagon-likepeptide1(GLP-1) receptor agonist
  - Dulaglutide (SC), liraglutide(SC), semaglutide (SC & oral)

General facts – oral agents

- All except alpha-glucosidase & DPP IV inhibitors
  - improve glycemic control to a similar degree
  - no clinical advantage to one class of drugs

- insulin secretagogues and α -glucosidase inhibitors begin to lower the plasma glucose immediately

- biguanides and thiazolidinediones effects are delayed by several weeks to months

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General facts – oral agents

- Not all agents are effective in all individuals with type 2 DM (primary failure)
- Insulin secretagogues cause hypoglycemia
  - Other agents do not directly cause hypoglycemia
- most individuals will eventually require treatment with more than one class of oral glucose-lowering agents or insulin
  - This reflects the progressive nature of type 2 DM

- **Because mechanisms of action of the first and second agents are different, the effect on glycemic control is usually additive**

- **If adequate control is not achieved with the combination of two agents add**
  - **a third oral agent**
  - **or insulin**

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Classification - Oral antidiabetic agents

- Insulin secretagogues
- Biguanides
- Thiazolidinediones
- α-glucosidase inhibitors
- Dipeptidyl peptidase IV inhibitors
- Sodium-glucose co-transporter 2 inhibitors
- GLP-1 receptor agonists (only semaglutide also SC)

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- **Insulin secretagogues**
  - **Sulfonylureas**
    - **1st Generation**
      - **Acetohexamide**
      - **Tolazamide**
      - **Tolbutamide**
      - **Chlorpropamide**

- 2nd Generation
  - Glyburide (glibenclamide)
  - Glipizide
  - Gliclazide
  - Glimepiride

- **Nonsulphonylureas**
  - **Repaglinide**
  - **Nateglinide**
  - **Mitiglinide**

- **Biguanides**
  - **Metformin**
- **Thiazolidinediones**
  - **Rosiglitazone**
  - **Pioglitazone**

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Sulfonylureas

- 2nd generation agents are preferred because they have less
  - adverse effects (eg hypoglycemia)
  - drug interactions
  - frequent administration

Sulfonylureas - Mech of action

- Stimulate insulin release from pancreatic β-cells

Pharmacokinetics

- t½ for chlorpropamide is 24-48 hrs (od)

- **Start with low doses and increase every 1-2 weeks based on self monitoring of blood glucose (SMBG)**

Adverse effects

- **Hypoglycemia**
  - Elderly patients
  - The longer the t½, the greater the risk of hypoglycemia
  - IV glucose infusion for 24-48 hrs
  - Asso with
    - Delayed meals
    - Increased physical activity
    - Alcohol intake
    - Renal failure

- **Weight gain**
  - **Due to increased insulin levels & improved glycemic control**

- **Contraindications**
  - Type 1 DM
  - Pregnancy
  - Lactation
  - Significant liver dysfunction
  - Renal dysfunction
    - Glyburide is not recommended
    - Glipizide and glimepiride should be initiated slowly to avoid hypoglycemia
  - Elderly patients (chlorpropamide)

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Repaglinide & nateglinide

- Mech of action = sulfonylureas
- Rapid onset of action
- Short duration of A
- ∴ Multiple preprandial use
- No sulfur

Metformin – Mech of action

- It ↑ the activity of the AMP-dependent protein kinase (AMPK)
  - ↑ glycogen storage in skeletal muscle
  - ↓ hepatic glucose production
  - ↑ insulin sensitivity
  - ↓ blood glucose

Metformin

- Does not cause hypoglycemia (an euglycemic agent)
    - no insulin release from the pancreas
- May promote some weight loss
    - For some patients there is no change in weight

Metformin – adverse effects

- 20% of patients
  - A, N, D, abdominal discomfort, metallic taste
  - Minimize by
    - ↑ drug doses slowly (adjust after 2-3 wks using SMBG)
    - taking the drug with meals
  - Transient, dose dependent

Metformin – adverse effects

- ↓ Vit B_{12} absorption
  - annual screening for deficiency

- Lactic acidosis (very rare, high doses)
  - Impaired hepatic metabolism of lactic acid

Metformin - Contraindications

- Renal impairment
- Hepatic disease
- Past history of lactic acidosis
- CCF
- Chronic hypoxic lung disease
- Alcoholism

Metformin

- Discontinue temporarily (& use insulin)
  - prior to IV contrast media
  - Severe illness

- All these conditions ↑ risk of lactic acidosis

Metformin

- Has potential benefit in patients with ASCVD

Thiazolidinediones

- Euglycemic agents
- Maximum clinical effects after 6-12 weeks of drug admin (act through gene regulation)

Thiazolidinediones

- Mech of action
- Activate insulin responsive genes that regulate carbohydrate & lipid metabolism
- Insulin must be present for these drugs to act

Thiazolidinediones

- **Mech of action**
- **↑ insulin sensitivity in tissues**
- **↑ glucose transport into muscle & lipid tissues by ↑ synthesis of glucose transporters**

T'diones – adverse effects

- Anemia
- Weight gain (2-3kg)
- Edema
  - ↓ renal sodium excretion
  - ↑ vascular permeability
- Plasma volume expansion
  - Discontinue if CCF develops
- Hepatotoxicity
- Macular edema (Rosiglitazone)

T'diones

- Monitor liver function every 2 months for the 1st year then periodically

- Additional methods of contraception as they interfere with met of oral contraceptives

T'diones

- Not used
  - Hepatic disease
  - If liver enzymes are elevated > 2.5Xs of upper limit of the normal
  - Previous LFT abnormality while on T'diones
  - Severe CCF
  - Pregnancy

T'diones

- Risk of bone fractures
- Bladder cancer (pioglitazone)
- Increased LDL cholesterol (rosiglitazone)

- In renal failure
  - No dose adjustment
  - Not recommended due to fluid retention

α-glucosidase inhibitors

- Mech of action
- Inhibit α-glucosidases in the intestine and slows the absorption of carbohydrates
- These enzymes convert starches & dissacharides to monosacharides

α-glucosidase inhibitors

- Do not stimulate insulin release ∴ no hypoglycemia (euglycemic)

- Reduce postprandial glucose

- **Used at the start of a meal**
  - Initially low dose at evening meal
  - Gradually increase dose over wks – months and administer with all meals

- **Don't use together with**
  - bile acid resins and antacids

α-glucosidase inhibitors

- If hypoglycemia occurs while on these drugs use glucose & not sucrose

α-glucosidase inhibitors

- **Adverse effects**
  - **Due to undigested carbohydrate in the colon that is fermented & releases gas**
  - **Malabsorption**
  - **Flatulence**
  - **Diarrhoea**
  - **Abdominal bloating**

α-glucosidase inhibitors

- Contraindicated
- Inflammatory bowel disease
- Gastroparesis
- Renal & liver impairment

Dipeptidyl peptidase IV inhibitors

- **Oral**
- **Sitagliptin, Saxagliptin, Vildagliptin**

- **Inhibits dipeptidyl peptidase IV (This enzyme degrades glucagon like polypeptide)**
  - **Potentiates glucose mediated insulin secretion**

- **Reduce dose in renal dysfunction**

Dipeptidyl peptidase IV inhibitors

- **Do not cause hypoglycemia**
- **No weight change**
- **Adjust dose in renal failure except for linagliptin**
- **AEs**
  - **Joint pain**
  - **May cause pancreatitis (discontinue)**

Sodium-glucose co-transporter 2 (SGLT2) inhibitors

- Glucose is filtered by the glomeruli and reabsorbed in the proximal tubules by sodium-glucose transporters (SGLTs)
- SGLT2 accounts for 90% of glucose reabsorption
- Inhibition of SGLT2 causes glycosuria and lowers glucose levels

SGLT2 inhibitors

- Canagliflozin
- Dapagliflozin
- Empagliflozin

SGLT2 inhibitors

- Used alone
- In combination with other oral agents or insulin
- Modest weight loss of 2–5 kg
- Do no cause hypoglycemia

SGLT2 inhibitors

- Efficacy is reduced in chronic kidney disease
  - Not used in severe renal disease

SGLT2 inhibitors - AEs

- Genital infections and UTIs
- Osmotic diuresis
  - Hypotension
  - Polyuria
  - Thirst
- ↑ LDL cholesterol
- Dapagliflozin
  - ? Breast cancer
  - ? Bladder cancer

Bile acid sequestrants

- Colesevelam
- Bind bile acids; mechanism of glucose lowering not known
- The most common side effects are gastrointestinal (constipation, abdominal pain, and nausea).
- The role of this class of drugs in the treatment of type 2 DM is not yet defined