

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

- 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, HF etc

- A sodium–glucose cotransporter 2 (SGLT2) inhibitor
 - Empagliflozin, canagliflozin, dapagliflozin
- or
- glucagon-like peptide 1 (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**

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

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)

- **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

- **α -glucosidase inhibitors**
 - **Acarbose**
 - **Miglitol**
 - **Voglibose**

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

- $t_{1/2}$ 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 $t_{1/2}$, 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)**

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 B₁₂ 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 $\therefore$ 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 not 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