



**North East and
North Cumbria**

Medications for Children and Young People Living with Type 2 Diabetes

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Treatment of Type 2 diabetes in children and young people

- Type 2 diabetes in youth is different not only from type 1 diabetes but also from type 2 diabetes in adults and has unique feature:
 - more rapidly progressive decline in β -cell function
 - accelerated development of diabetes complications
- Type 2 diabetes disproportionately impacts youth of ethnic and racial minorities and can occur in complex psychosocial and cultural environments, which may make it difficult to sustain healthy lifestyle changes and self-management behaviours.
- Treatment should include:
 - lifestyle management
 - diabetes self-management education and support
 - pharmacologic treatment

NICE guideline pharmacological recommendations-Blood Glucose

Metformin 1st line

Offer insulin if:

- HbA1c 69mmol/mol or more
- Basal-bolus if they have ketosis but not DKA

Offer liraglutide or dulaglutide in addition to metformin in CYP aged over 10 years if:

- an HbA1c level of more than 48 mmol/mol (6.5%) or
- a plasma glucose level of more than 7 mmol/litre, on 4 or more days a week, when fasting or before meals or level of more than 9 mmol/litre, on 4 or more days a week, 2 hours after meals.

Consider SGLT2 in CYP aged over 10 years if:

- They meet criteria above for GLP-1
- Are not able to tolerate the GLP-1 or have a clear preference for SGLT2
- **Dapagliflozin is licensed for type 2 DM in CYP 10 years or older, Empagliflozin is not in the UK but is in the US.**

Diabetes Care. 2022;46(Supplement_1):S230-S253. doi:10.2337/dc23-S014

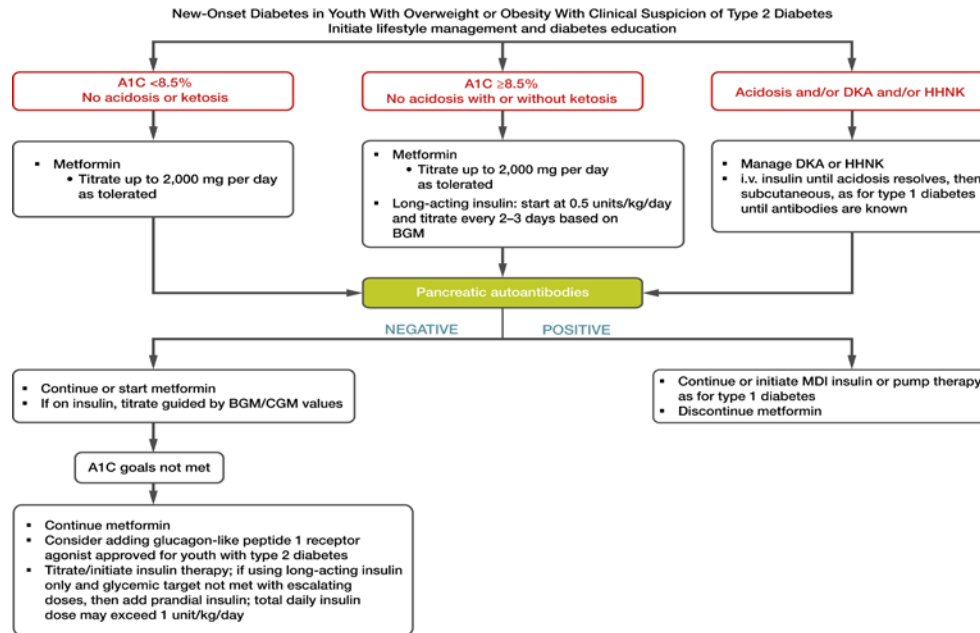
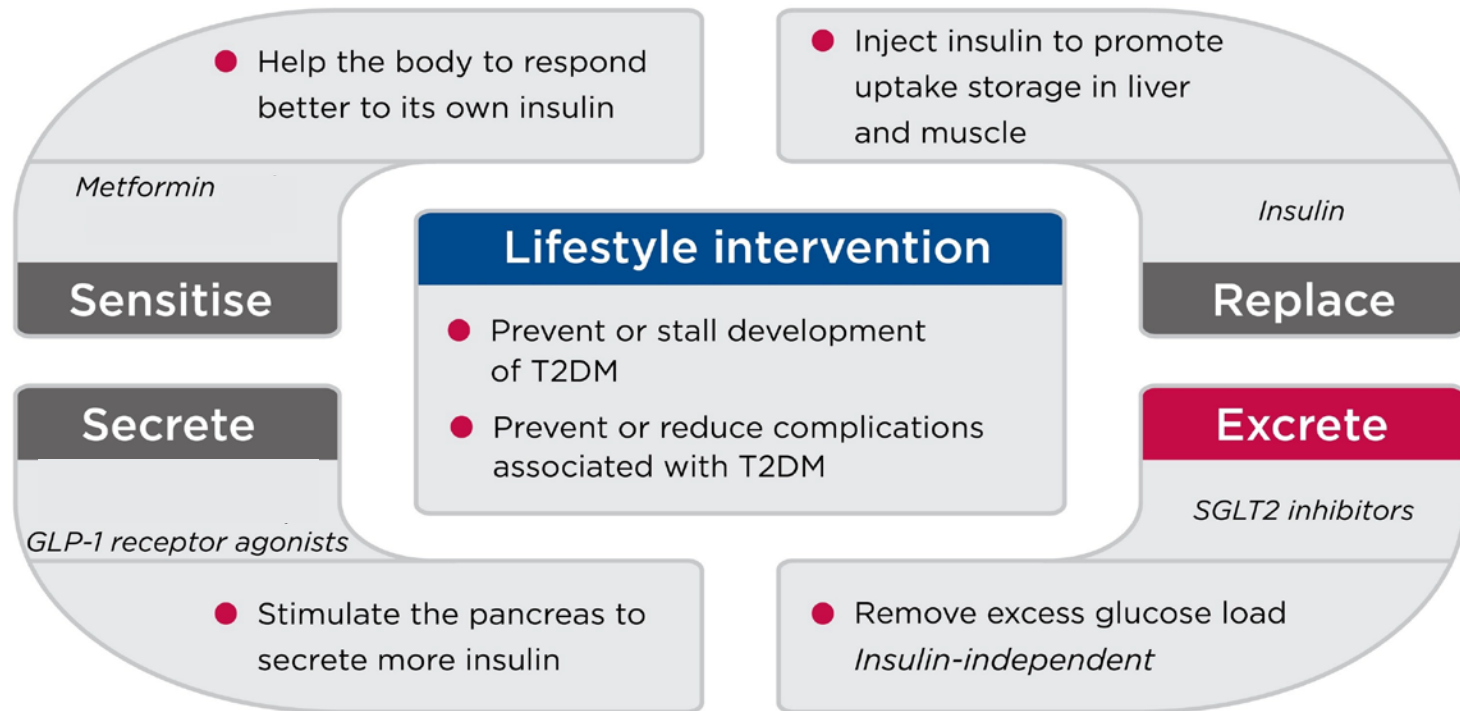


Figure Legend:

Management of new-onset diabetes in youth with overweight or obesity with clinical suspicion of type 2 diabetes. A1C 8.5% = 69 mmol/mol. Adapted from the ADA position statement “Evaluation and Management of Youth-Onset Type 2 Diabetes” (3). BGM, blood glucose monitoring; CGM, continuous glucose monitoring; DKA, diabetic ketoacidosis; HHNK, hyperosmolar hyperglycemic nonketotic syndrome; i.v., intravenous; MDI, multiple daily injections.

Treatment options for controlling excess blood glucose in type 2 diabetes





Metformin

Metformin

Characteristics that may guide individualised treatment choices

Primary physiological action(s)	Advantages	Disadvantages/ adverse effects	Efficacy	Significant Drug Interactions	Counselling Points
<ul style="list-style-type: none"> • ↓ Hepatic glucose production • Multiple other non-insulin-mediated mechanisms 	<ul style="list-style-type: none"> • Extensive experience • No hypoglycaemia • Inexpensive • Reduces insulin resistance 	<ul style="list-style-type: none"> • GI symptoms • Taste altered • Vitamin B₁₂ deficiency • Use with caution or dose adjustment for CKD stage 3B • STOP if eGFR <30ml/min • Lactic acidosis (rare) 	<ul style="list-style-type: none"> • High 	<ul style="list-style-type: none"> • Nephrotoxics (e.g. NSAIDs, ACEi, diuretics, ARBs) • Iodinated contrast media 	<ul style="list-style-type: none"> • Take with or just after food or a meal • Do not chew, swallow tablets whole • Sick day rules



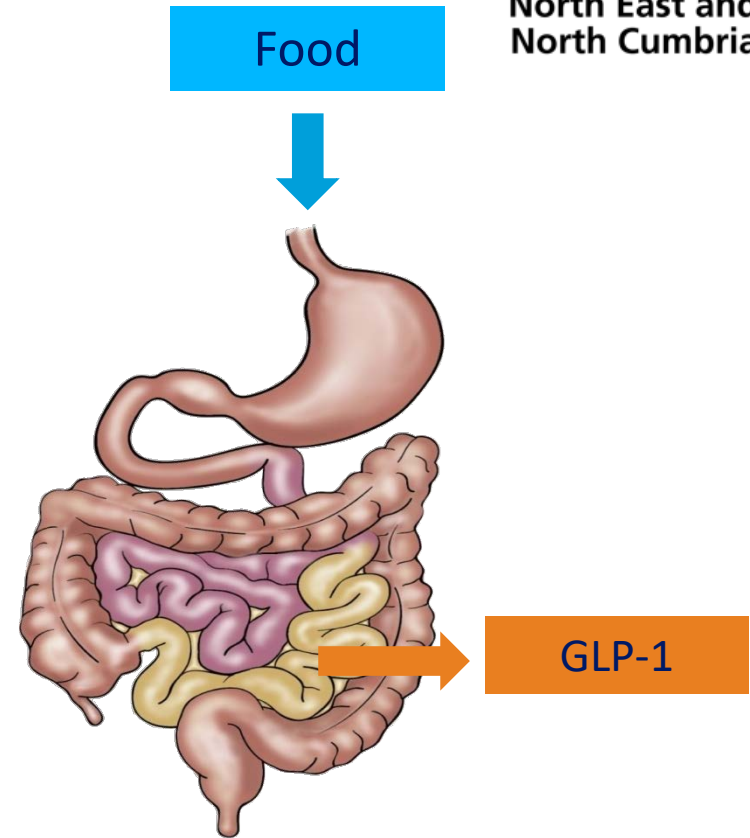
**Glucagon-like peptide-1
(GLP-1)**

Glucagon-like peptide-1

GLP-1 is a naturally occurring incretin hormone

GLP-1 is released from intestinal L cells in response to eating

GLP-1 secretion is impaired in people with T2DM



GLP1 – effects beyond glycaemic control

Pancreas

- ↑ Beta-cell function^{1*}
- ↓ Beta-cell death¹
- ↑ Insulin production^{1*}
- ↓ Glucagon secretion¹



Brain

- ↓ Body weight^{5*}
- ↓ Food intake⁶
- ↓ Appetite^{7,8}



Incretin system

Replacement of deficient
GLP-1 response⁹

- ↓ Glucose production¹⁰
- ↑ Insulin sensitivity¹⁰
- ↓ Conversion carbohydrate to fat¹⁰
- ↓ Accumulation of lipids¹⁰
- ↓ Retention of lipids¹¹



GLP-1RA



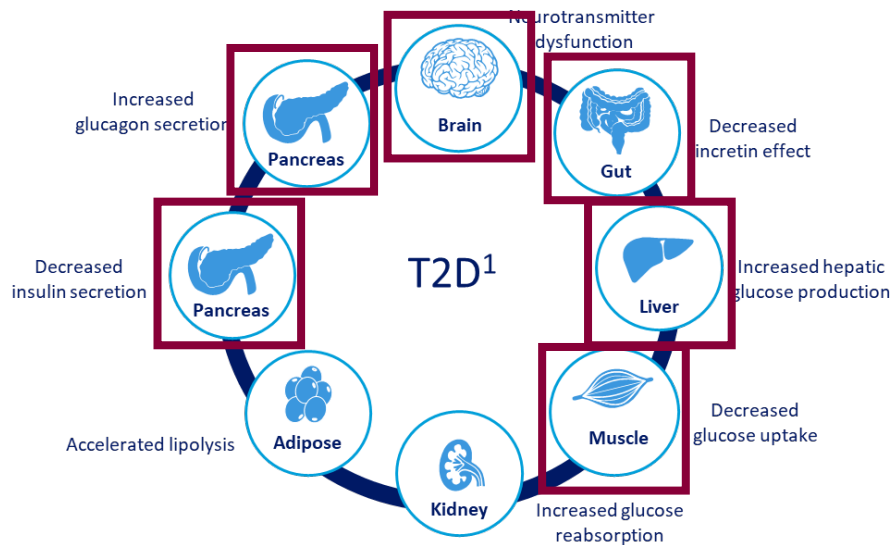
- ↓ Cardiovascular risk²
- ↓ Fatty acid metabolism³
- ↑ Cardiac function³
- ↓ Systolic blood pressure³
- ↓ Inflammation⁴
- ↓ Plaque progression⁴

Heart



Liver

Pathogenesis – GLP-1



	GLP-1 receptor agonists
Pancreas beta-cell function	Improved pancreatic beta-cell function ^{2,3}
Pancreas alpha-cell function	Inhibits glucagon secretion from alpha-cell in the presence of high glucose ⁴
Gut	Increased incretin effects, reduced gastric emptying ⁵
Brain	Reduced hunger and energy intake in the brain ⁵
Liver	With lower glucagon, hepatic glucose production can be reduced ²
Muscle	Increased insulin sensitivity ¹
Kidney	

PO Semaglutide

Starting dose

1.5
mg Start with 3 mg once daily for 1 month



Maintenance doses

4
mg Increase dose to 7 mg once daily for at least 1 month

9
mg Based on individual needs, may increase dose to 14 mg once daily

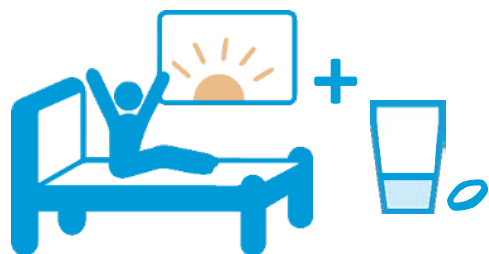


- Tablets should **not be split, crushed or chewed**, as it is not known whether this impacts absorption of semaglutide
- Taking two 7 mg tablets to achieve the effect of a 14 mg dose has not been studied and is therefore **not recommended**
- Store in the **original blister package** in order to protect from light and moisture.
- This medicinal product does **not require** any special temperature storage conditions



Please note these are the new Rybelsus strengths due to a change in formulation

Oral dosing - Counselling



Take on an **empty stomach** upon waking, with a **sip of water** (no more than 120 mL)



Wait at least **30 minutes** before eating, drinking, or taking any other oral medication



Taken **whole** and **not** to be **split**, **crushed** or **chewed**

GLP-1

Primary physiological action(s)	Advantages	Disadvantages/ adverse effects	Efficacy
<ul style="list-style-type: none"> • Glucose dependent: <ul style="list-style-type: none"> ↑ Insulin secretion ↓ Glucagon secretion • ↑ Satiety 	<ul style="list-style-type: none"> • Low risk of hypoglycaemia as monotherapy • ↓ Weight • ↓ Postprandial glucose excursions • Improves cardiovascular risk factors • ↓ MACE with some agents • ↓ Albuminuria with some agents • Greater lowering of fasting glucose vs short-acting preparations • Once-weekly dosing (except daily liraglutide) 	<ul style="list-style-type: none"> • GI side effects, including gall bladder disease • ↑ Heart rate • Training requirements • Dose adjustment/ avoidance for some agents in renal disease • Acute pancreatitis (rare/uncertain) • C cell hyperplasia/ medullary thyroid tumours (rare/ uncertain; observed in animals only) • Alopecia • Very high cost 	<ul style="list-style-type: none"> • High-very high

Example(s) of medication(s) within the class: dulaglutide; exenatide extended-release; liraglutide; semaglutide ▼.

GLP-1 RA in CYP for obesity

Adolescents (≥ 12 years)

Wegovy (Semaglutide) and Saxenda (Liraglutide) are indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adolescents ages 12 years and above with

- obesity and
- body weight above 60 kg

Treatment with Wegovy should be discontinued and re-evaluated if adolescent patients have not reduced their BMI by at least 5% after 12 weeks on the 2.4 mg or maximum tolerated dose.

Treatment with Saxenda should be discontinued and re-evaluated if patients have not lost at least 4% of their BMI or BMI z score after 12 weeks on the 3.0 mg/day or maximum tolerated dose.

Mounjaro is not licensed for treatment of obesity in adolescents

Tips for people with GI side effects

The most common side effects observed in clinical trials were nausea and diarrhoea

Generally, these were **mild/moderate** in severity, of **short duration** and most frequently reported during the **first few months on treatment**

Encourage patients to try:

- ✓ Eating smaller portions
- ✓ Eating slowly
- ✓ Stay hydrated
- ✓ Stop eating at first sign of fullness

Encourage patients to avoid:

- ✗ Large portions
- ✗ Fried or fatty foods
- ✗ Overly sweet or spicy foods
- ✗ Drinking alcohol and smoking cigarettes

GLP-1 receptor agonists side effects and potential for misuse

Inform patients about the common risk of gastrointestinal side effects which can lead to more serious complications such as severe dehydration, resulting in hospitalisation.

Hypoglycaemia can occur even in non-diabetic patients, ensure patients are aware of the symptoms and signs of hypoglycaemia and to urgently seek medical advice.

Warn patients of the risk of falsified GLP-1RA medicines for weight loss.

There have been reports of potential misuse of GLP-1RAs for unauthorised indications such as aesthetic weight loss.

Report suspected adverse drug reactions and falsifications to the [Yellow Card](#) scheme.

GLP-1 receptor agonists: reminder of the potential side effects and to be aware of the potential for misuse

Healthcare professionals are reminded to inform patients about the common and serious side effects associated with glucagon-like peptide-1 receptor agonists (GLP-1RAs).

Glucagon-like peptide-1 (GLP-1) agonists and oral contraception



FSRH recommendations

- Individuals should be advised to use contraception whilst using GLP-1 agonists.
- Individuals using tirzepatide and oral contraception should switch to a non-oral contraceptive method, or add a barrier method of contraception, for four weeks after initiation and for four weeks after each dose increase.
- There is no need to add a barrier method of contraception when using semaglutide, dulaglutide, exenatide, lixisenatide or liraglutide.
- Individuals who experience severe diarrhoea or vomiting during use of GLP-1 agonists should follow existing [FSRH recommendations](#).

Preconception advice

GLP-agonist	Washout period
Tirzepatide	One month ⁶
Semaglutide	Two months ¹
Exenatide	12 weeks ²

Table 1. Washout periods of GLP-1 agonists

[CEU-statement-GLP-1-agonists-and-contraception.pdf](#)

[Injectable weight loss drugs, contraception and HRT – summary with practical action plan | Primary Care Women's Health Society](#)

Mood changes with GLP-1s

- The role of GLP-1s in psychiatric outcomes, particularly in depression or anxiety disorder, presents a mixed picture.
- One large 2024 study in the journal [Scientific Reports](#) found that people with obesity who were on GLP-1s had a slightly elevated risk of anxiety and suicidal behaviour when compared with controls and almost double the risk of major depression.
- On the other hand, a 2024 [study](#) led by Thomas A. Wadden, PhD—and funded by Novo Nordisk, found that GLP-1 takers without known psychopathology weren't any more likely to develop depression or suicidal thoughts or actions than controls. They even had a “small but statistically significant” reduction in depressive symptoms
- Another [study](#) highlights that establishing a clear cause-and-effect link between metabolic diseases, depression and medications is difficult because of their possible reciprocal relationship, shared underlying mechanisms and individual differences.
- It's a complex area involving behaviours, emotions, physical changes and an area that requires more research but where the input from psychologists can be vital.



Tirzepatide (Mounjaro)

Tirzepatide (Mounjaro)

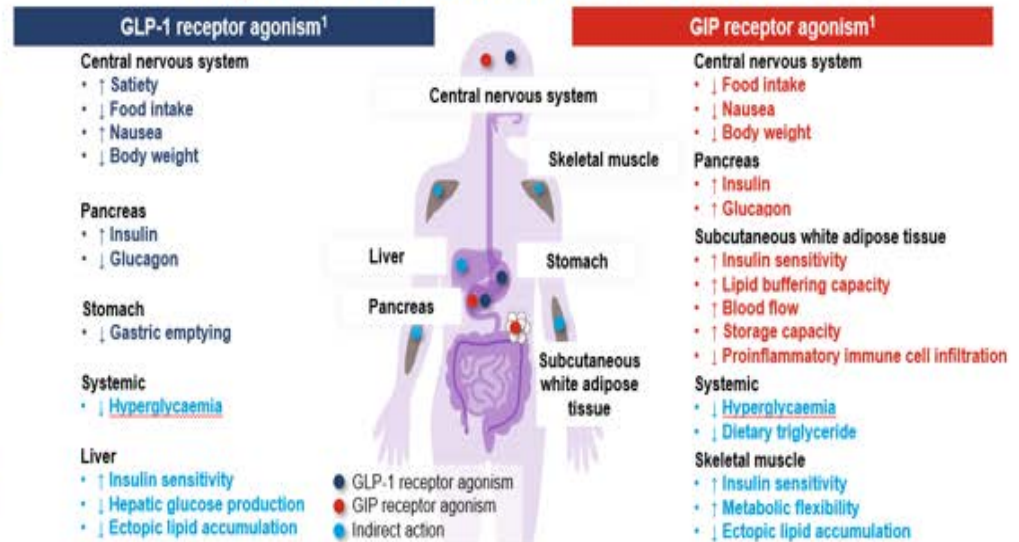
The first and only licensed GIP (Glucose-dependent insulinotropic polypeptide) and GLP-1 receptor agonist

In the Surpass trials Mounjaro 5mg, 10mg and 15mg demonstrated superior mean weight reductions vs Semaglutide **1mg** at 40 weeks

At 15mg Mounjaro delivered double the mean weight reductions vs Semaglutide **1mg** at week 40 (6.2kg vs 12.4kg)

Trials did show increased weight loss with higher doses of semaglutide (7% weight loss in 1mg group and 9.6% in 2.4mg group at 28 weeks).

Proposed effects of incretins on the body



Disclaimer: Actions of GIP mentioned above are proposed and based on clinical and preclinical studies and not all have been confirmed in humans. Data presented in this figure come from human and animal studies.

GIP=Glucose-dependent Insulinotropic Peptide; GLP-1=Glucagon-like Peptide-1
Santoro RJ, et al. Trends Endocrinol Metab. 2020;31(6):410-421.

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1. Friás JP, et al. *N Engl J Med.* 2021;385(8):503-515.
2. Mounjaro® Summary of Product Characteristics.

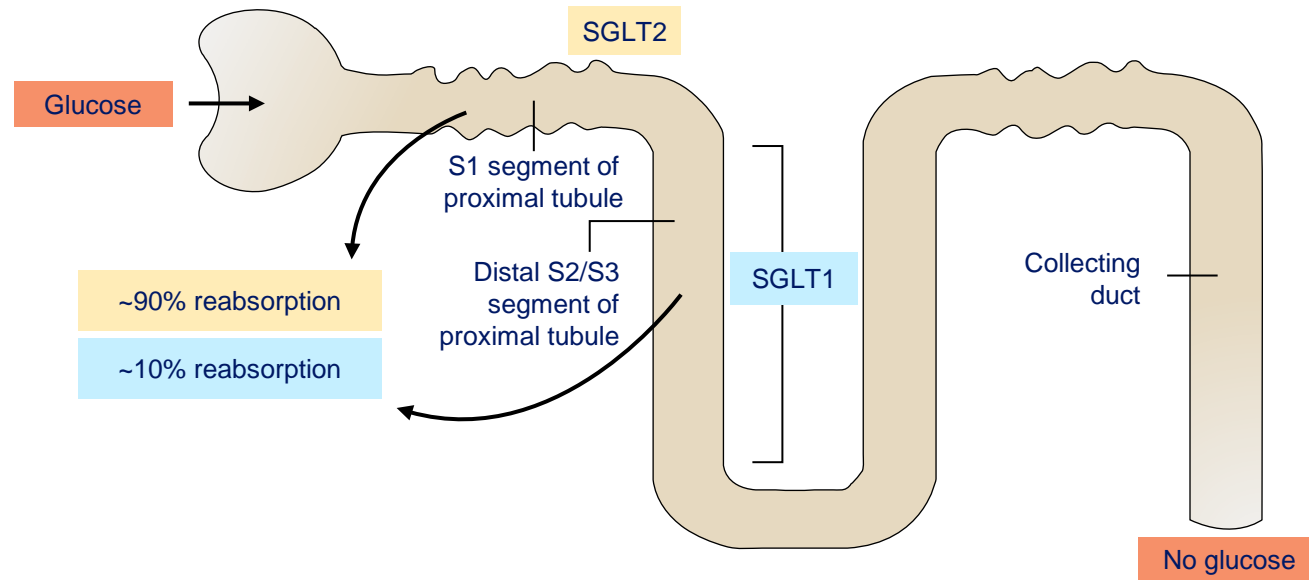
Mounjaro phase 3 trials in children and adolescents with type 2 diabetes

- The trial met the primary endpoint of superior A1C reduction with Mounjaro compared to placebo at 30 weeks, lowering A1C by an average of 2.2% from an average baseline of 8.05%
- In a key secondary endpoint, 86.1% of participants randomized to the 10 mg dose of Mounjaro achieved a target A1C of $\leq 6.5\%$.
- Mounjaro showed clinically meaningful improvements in BMI
 - The 10 mg dose of Mounjaro reduced BMI by 11.2% on average at 30 weeks.
- Improvements in A1C and BMI reductions continued through 52 weeks in the trial's long-term extension.



**Sodium Glucose
Transport Inhibitors
(SGLT2s)**

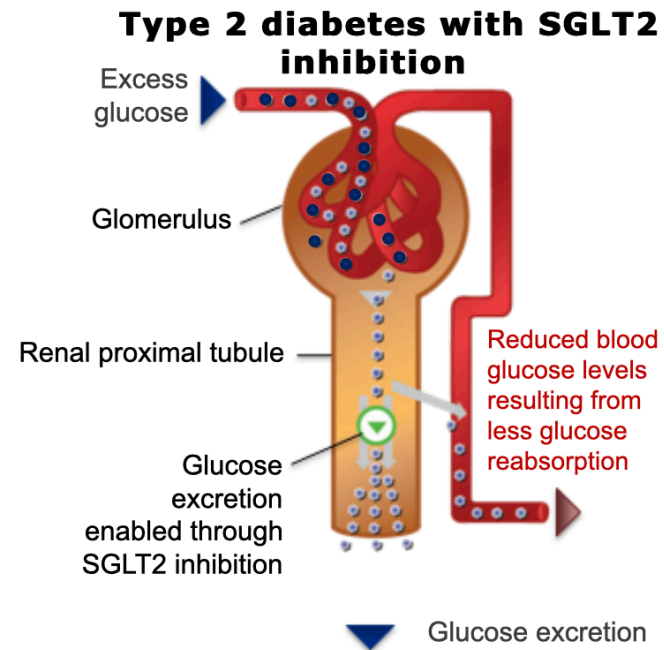
How SGLT2 inhibitors work: Glucose reabsorption in the kidney



The primary site for reabsorption in the kidney is the first segment of the proximal tubule

How SGLT2 inhibitors work: Glucose reabsorption in the kidney

- Inhibit proximal tubular reabsorption
- Causes diuresis
- Causes natriuresis (Na excretion)
 - For each molecule of glucose excreted a molecule of sodium is excreted
- Low BP
- Low weight
- Reno-protective



SGLT2 inhibitors

Characteristics that may guide individualised treatment choices

Primary physiological action(s)	Advantages	Disadvantages/ adverse effects	Efficacy
<ul style="list-style-type: none">• Blocks glucose reabsorption by the kidney, increasing glucosuria• ? Other tubulo-glomerular effects	<ul style="list-style-type: none">• No hypoglycaemia if not used with SU/insulin• ↓ Weight• ↓ Blood pressure• Effective at all stages of T2D with preserved glomerular function• ↓ MACE, HF, CKD with some agents	<ul style="list-style-type: none">• Genital infections• Urinary tract infection• Polyuria• Volume depletion/ hypotension/dizziness• ↑ LDL-C• ↑ Creatinine (transient)• Dose adjustment/ avoidance for renal disease• ↑ Risk for amputation (canagliflozin)• ↑ Risk for fracture (canagliflozin)• ↑ Risk for DKA (rare)• Fournier's gangrene (rare)• Expensive	<ul style="list-style-type: none">• Intermediate-high (dependent on GFR)

Example(s) of medication(s) within the class: canagliflozin; dapagliflozin; empagliflozin; ertugliflozin.

Thank you

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