PEER REVIEWED FEATURE

Youth-onset type 2 diabetes

The ever-changing face of pharmacotherapy

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Youth-onset type 2 diabetes follows a more aggressive course than adult-onset disease, with earlier complications and faster decline in beta-cell function. Improved understanding of its pathophysiology and expanding pharmacotherapy options are changing the approach to personalised management.

KEY POINTS

- Youth-onset type 2 diabetes (YOT2D) follows a more aggressive course than adult-onset type 2 diabetes, with earlier complications and more rapid decline in beta-cell function.
- Lifestyle intervention remains the cornerstone of management, but pharmacotherapy should be intensified promptly to achieve and maintain glycaemic targets.
- Metformin remains first-line therapy for most young people with YOT2D, with insulin used during metabolic decompensation and as rescue therapy when required.
- Sodium-glucose cotransporter-2 inhibitors, glucagon-like peptide-1 receptor agonists and tirzepatide are expanding treatment options and improving glycaemic control in YOT2D.
- Treatment should be individualised according to the patient's clinical presentation, comorbidities, treatment goals and preferences.

Youth-onset type 2 diabetes (YOT2D) is increasing globally, with the highest burden occurring in First Nations populations. Aboriginal and Torres Strait Islander children have an 18-fold higher risk of developing YOT2D than non-Indigenous children.[1] The US SEARCH for Diabetes in Youth Study predicts a sixfold increase in YOT2D by 2050.[2]

YOT2D follows a more aggressive course than adult-onset type 2 diabetes (T2D), with earlier onset of complications and a more rapid decline in beta-cell function.[2] It remains uncertain whether newer pharmacotherapies will alter this trajectory, as earlier cohorts treated with a limited range of agents experienced consistently poor outcomes. Growing evidence has improved our understanding of the complex pathophysiology of T2D and highlighted important differences between YOT2D and adult-onset T2D, including responses to pharmacotherapy. Many drug classes well established in adult-onset T2D management have now been evaluated in young people with YOT2D for pharmacokinetics, pharmacodynamics, glycaemic efficacy and safety, expanding the range of potential treatment options.

This article reviews the unique pathophysiology of YOT2D, current treatment targets and the evolving glycaemic-lowering pharmacotherapy options available to support individualised care.

The complex pathophysiology of T2D

A detailed understanding of the pathophysiology of T2D enables rational selection of combination therapies that target the multiple organs and tissues involved. Reduced insulin sensitivity in the liver, skeletal muscle and adipose tissue initially leads to compensatory hyperinsulinaemia. As pancreatic beta-cell function progressively declines, insulin secretion becomes inadequate, resulting in hyperglycaemia, the hallmark of T2D (Figure 1). Insulin resistance is driven by genetic factors, reflected by the clustering of T2D within families, as well as elevated

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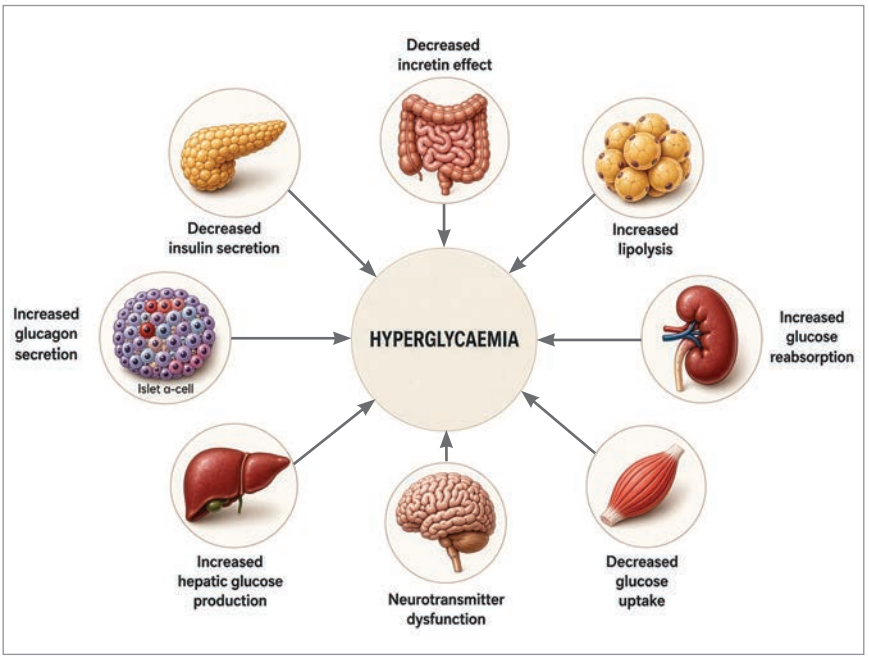

Figure 1. Hyperglycaemia: the result of eight pathophysiological defects.

1. KEY PATHOPHYSIOLOGICAL DEFECTS IN TYPE 2 DIABETES

Excess body fat
Adipose tissue becomes resistant to insulin's antilipolytic effects, resulting in elevated FFA levels. FFAs stimulate gluconeogenesis, promote hepatic and skeletal muscle insulin resistance, and impair insulin secretion, a process known as lipotoxicity. Dysfunctional adipose tissue also produces excessive amounts of inflammatory and atherogenic cytokines that further worsen insulin resistance.

Skeletal muscle
Skeletal muscle is the primary site of exogenous glucose disposal. GLUT4 is the major transporter involved. Insulin and exercise stimulate translocation of GLUT4 to the muscle cell membrane, facilitating glucose uptake. In T2D, skeletal muscle insulin resistance impairs glucose uptake, contributing to hyperglycaemia.

Liver
Hepatic IR is characterised by excessive basal hepatic glucose production despite elevated fasting insulin levels and inadequate suppression of glucose output after meals due to reduced hepatic responsiveness to insulin.

Incretins
GLP-1 and GIP account for most of the incretin effect following food intake by stimulating insulin secretion. In T2D, GLP-1 secretion is reduced and resistance to the actions of GIP develops.

Pancreas
In the setting of insulin resistance, beta cells initially increase insulin production, resulting in compensatory hyperinsulinaemia. As beta-cell capacity declines, postprandial and subsequently fasting hyperglycaemia develop, with up to 80% of beta-cell function lost by the time of diagnosis. The exact mechanisms underlying beta-cell failure remain uncertain, but several processes are thought to contribute, including excess deposition of lipids within beta cells and elevated FFA levels (lipotoxicity), which impair insulin secretion and accelerate beta-cell failure, and chronic hyperglycaemia (glucotoxicity), which further impairs beta-cell function and reduces insulin production. In addition, suppression of postprandial glucagon secretion from pancreatic alpha cells is impaired in T2D.

Kidneys
About 90% of filtered glucose is reabsorbed in the proximal convoluted tubule via sodium-glucose cotransporter-2. Renal glucose reabsorptive capacity is increased in people with T2D compared with matched healthy controls.[3]

Brain
The brain contributes to T2D through central insulin resistance and impaired regulation of appetite and energy balance.

Abbreviations: FFA = free fatty acid; GLUT4 = glucose transporter 4; GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide-1; T2D = type 2 diabetes.

adiposity, ectopic fat deposition, sedentary behaviour and the physiological insulin resistance associated with puberty. The major organs and tissues involved in T2D pathophysiology are outlined in Box 1.[3]

How does YOT2D differ from adult-onset T2D?

Although YOT2D and adult-onset T2D share many core pathophysiological defects, important differences exist (Figure 2). Young people have greater insulin resistance than adults with the same body mass index (BMI), body fat percentage, ethnicity and sex.[4,5] They also have lower insulin clearance and a greater beta-cell insulin secretory response after adjustment for insulin resistance. YOT2D occurs more commonly in females, likely because of the physiological insulin resistance associated with the additional growth hormone secretion seen during puberty, whereas adult-onset T2D is more common in males. Alpha-cell dysfunction also appears to be less pronounced in YOT2D.[6]

The Restoring Insulin Secretion (RISE) study examined whether early treatment could preserve or restore beta-cell function in people with glucose intolerance or newly diagnosed T2D. Neither metformin nor basal insulin preserved beta-cell function in youth, whereas beta-cell function was maintained in adults.[7] Durable glycaemic control is therefore more difficult to achieve in YOT2D, as many therapies are less effective in the setting of severe insulin resistance.[8]

The phenotypes of YOT2D

YOT2D is a heterogeneous condition with distinct metabolic subtypes that require personalised approaches to management. Clustering analyses of routine clinical measures have identified three main subtypes: obesity-related YOT2D, insulin-deficient YOT2D and insulin-resistant YOT2D. The insulin-deficient and insulin-resistant subtypes together account for about half of all cases and are associated with greater disease severity and higher

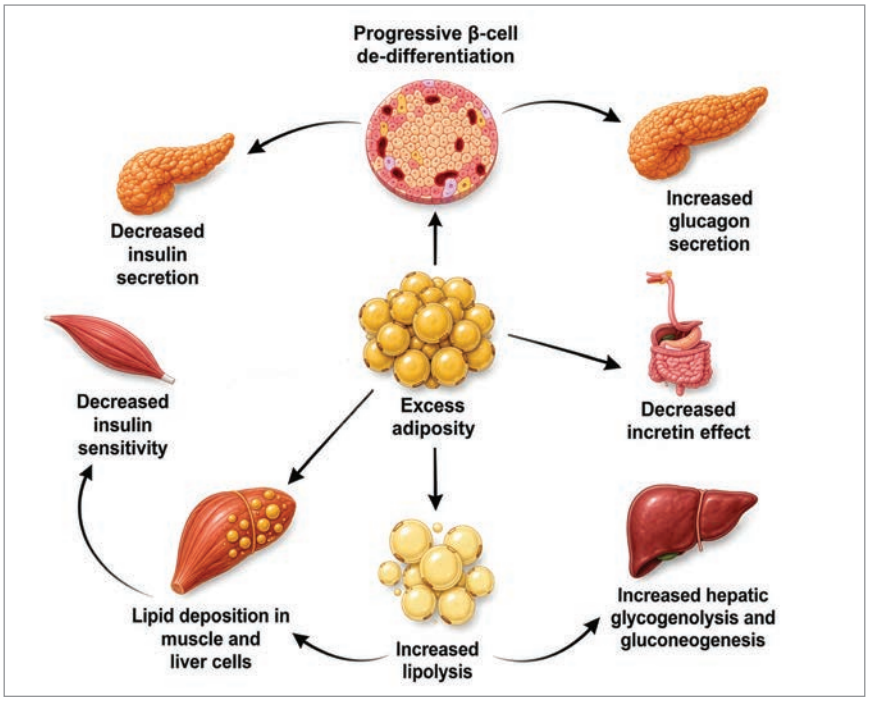

Figure 2. Pathophysiology of youth-onset type 2 diabetes. Multiple mechanisms involving pancreatic beta-cells and liver, muscle and adipose tissue contribute to hyperglycaemia and the development of type 2 diabetes. Youth with type 2 diabetes exhibit greater insulin resistance, more aggressive beta-cell failure and more rapid glycaemic deterioration than adults with type 2 diabetes.

rates of treatment failure.[9,10] Beta-cell decline varies widely (6 to 30% per year) and is influenced by age at diagnosis, ethnicity, genetics, glycated haemoglobin (HbA_{1c}) level, BMI and the presence of islet autoantibodies.[11,12]

Glycaemic targets

A target HbA_{1c} level of 6.5% or less is recommended for young people with YOT2D. HbA_{1c} level should be measured every three months and therapy intensified as needed to maintain the target (a treat-to-target approach), rather than waiting for glycaemic control to deteriorate before escalating treatment (a treat-to-failure approach). This target reflects the accelerated rate of complications and higher mortality associated with YOT2D compared with adult-onset T2D and childhood type 1 diabetes.

To achieve this target, recommended glucose levels are 4 to 6 mmol/L fasting and 4 to 8 mmol/L two hours postprandially. Self-monitoring of blood glucose should be individualised, and continuous glucose monitoring can be a useful adjunct in YOT2D, improving the proportion of time spent within the target glucose range.[13]

Choosing pharmacotherapy in YOT2D

When add-on therapy is required to achieve glycaemic targets, the patient's engagement and adherence should first be assessed. Additional factors must then be considered, and each medication change should be accompanied by education regarding administration, expected glycaemic effects, adverse effects, safety considerations, follow up and stopping criteria. Several medications have minimum approved ages because of limited research data or TGA approval requirements; however, off-label use may sometimes be appropriate with careful monitoring. Key factors influencing treatment selection are outlined in Box 2. The choice of pharmacotherapy at diagnosis depends on the clinical presentation and should follow current International Society for Pediatric and Adolescent Diabetes recommendations (Figure 3).[14] The key characteristics of currently available pharmacotherapies for YOT2D are summarised in the Table.[15-55]

Pharmacotherapy should complement lifestyle modification and support reversal of the underlying disease mechanisms. Improvements in body composition,

2. FACTORS TO CONSIDER IN INDIVIDUALISING ANTIHYPERGLYCAEMIC THERAPY

Patient-specific clinical factors
- Age
- Sex
- Pubertal status
- Comorbidities
- Chronic diseases (renal, liver, cardiac)
- Baseline investigations required
- Contraindications
- Allergies
- Potential drug interactions
- Ongoing surveillance required

Medication-specific factors
- Glycated haemoglobin-lowering efficacy
- Mechanism of action
- Impact on weight
- Side-effect profile
- Hypoglycaemia risk
- Blood glucose monitoring requirements
- Route of administration
- Dosing schedule
- Storage requirements

Patient, family and treatment goals
- Patient and family preferences
- Ability to adhere to treatment
- Education and support needs
- Level of supervision required
- Cost and access
- Sexual activity and contraception counselling
- Treatment goals (glycaemia, weight, comorbidity targets)
- Duration of therapy

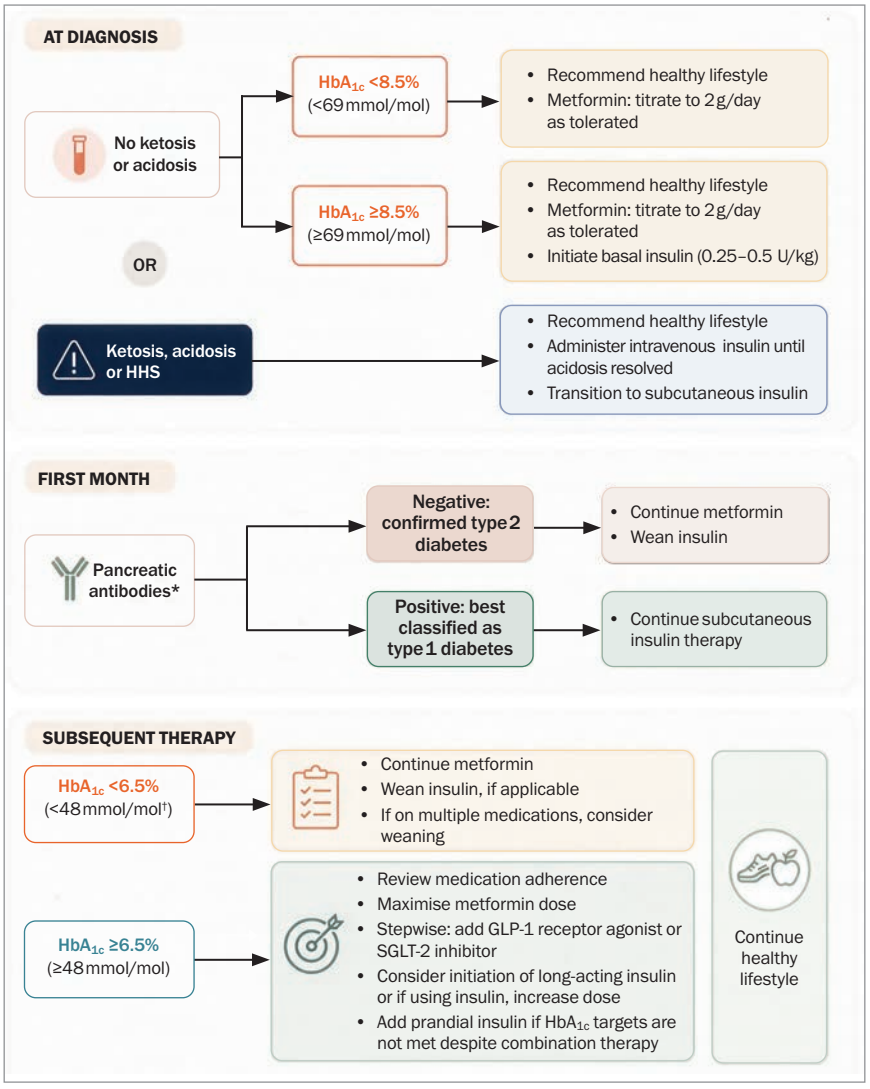

Figure 3. Evaluation and management of new-onset type 2 diabetes.

Abbreviations: HbA_{1c} = glycated haemoglobin; HHS = hyperosmolar hyperglycaemic state; GLP-1 = glucagon-like peptide-1; SGLT-2 = sodium-glucose cotransporter-2.

* If pancreatic autoantibodies are not available, use family history, response to treatment, clinical progression and associated metabolic comorbidities to establish diabetes type.

† HbA_{1c} target may be ≥6.5% in specific circumstances (significant hypoglycaemia).

Modified from 2024 International Society for Pediatric and Adolescent Diabetes (ISPAD) Clinical Practice Consensus Guidelines.

achieved through reducing excess body fat while maintaining or increasing skeletal muscle mass, can substantially reduce insulin resistance. Adequate sleep, regular moderate- to vigorous-intensity physical activity, reduced sedentary behaviour and a nutrient-rich diet are all essential components of management. Ongoing support is required to help young people maintain these lifestyle measures, and involvement of a multidisciplinary team experienced in managing YOT2D is recommended.

Biguanides

Metformin is first-line therapy for most young people with YOT2D and is generally well tolerated. It should only be initiated after resolution of ketosis or a hyperosmolar hyperglycaemic state.[14] When combined with insulin at diagnosis, metformin may facilitate more rapid insulin withdrawal over the following weeks. About half of adolescents with YOT2D can maintain long-term glycaemic control with metformin monotherapy compared with more than 80% of adults, who achieve glycaemic targets with metformin alone.[20,56] Metformin should be avoided in young people with intolerable adverse effects, known allergy to biguanides or significant renal impairment.

The recommended starting dose is metformin extended-release 500 mg with the evening meal or metformin immediate-release 250 mg once daily in younger children to improve tolerability.[14] The dose should be titrated over three to four weeks as tolerated to a maximum dose of 2 g daily. Metformin should be discontinued 48 hours before elective surgery, radiological studies involving iodinated contrast media and during significant gastrointestinal illness. Gastrointestinal adverse effects are common when commencing metformin; gradual dose escalation, administration with food and good adherence may help minimise these symptoms.[22]

Insulin

Insulin is used to manage hyperglycaemia associated with metabolic decompensation at diagnosis and may also be required later in the disease course. It often functions as a short-term 'rescue' therapy and should be discontinued as soon as clinical stabilisation permits. Insulin therapy can rapidly improve glycaemic control and is associated with low rates of symptomatic hypoglycaemia in YOT2D. Long-acting basal insulin is commenced first, with prandial insulin added if glycaemic targets are not achieved.

Where possible, insulin doses should be reduced by 30 to 50% each week and ceased once glycaemic targets are maintained, transitioning to metformin monotherapy in newly diagnosed patients or when another glucose-lowering agent is introduced. Discontinuing insulin where appropriate may help minimise weight gain. The Treatment Options for Type 2 Diabetes in Adolescents and Youth

TABLE. PHARMACOTHERAPIES FOR YOUTH-ONSET TYPE 2 DIABETES

Drug class*	Medication	Mechanism of action	Usual dose	Common adverse effects	HbA_{1c} reduction versus placebo	Weight and cardiometabolic effects	Clinical role in YOT2D	TGA approval/ pregnancy category
Biguanide[15-30]	Metformin, immediate release/ extended release	Suppresses hepatic glucose production and lipogenesis; increases glucose uptake and fat oxidation in muscle and adipose tissue; slows intestinal glucose absorption	250–2000 mg/ day orally	Abdominal pain, nausea, diarrhoea, reduced appetite, headache, vitamin B12 deficiency. Rare lactic acidosis during acute illness or dehydration	0.7–1.2%	Improved lipid profile; reduced BMI and adiposity	First-line therapy; can be combined with all other drug classes	Approved for age ≥10 years; pregnancy category C
Insulin[31-34]	Basal, bolus and premixed	Increases peripheral glucose uptake and suppresses hepatic glucose production	Variable dose and frequency; SC injection	Hypoglycaemia, weight gain. Rare: severe hypoglycaemia, hypersensitivity reactions	0.6–5.2%	Increased BMI	Initial treatment in DKA and HHS; rescue therapy during metabolic decompensation; long-term therapy in insulin-deficient YOT2D	Most preparations approved for YOT2D; pregnancy category A or B
SGLT-2 inhibitor[35-43]	Empagliflozin	Inhibits renal glucose reabsorption in the proximal tubule, increasing urinary glucose excretion; undergos biotransformation in the liver and excreted renally	5–25 mg daily orally	Genitourinary infections, dehydration, headache, nasopharyngitis; hypoglycaemia when combined with insulin; rare: euglycaemic DKA	0.84% (26 weeks)	No significant BMI reduction in YOT2D; cardiovascular and renal benefits have been demonstrated in adults	Second-line therapy	Approved for age ≥10 years; pregnancy category D
	Dapagliflozin		5–10 mg daily orally		0.75% (24 weeks; NS)			Approved for age ≥18 years; pregnancy category D
GLP-1 receptor agonist[44-54]	Dulaglutide	Enhances glucose-dependent insulin secretion, suppresses glucagon secretion, delays gastric emptying and increases satiety	0.75–1.5 mg weekly; SC injection	Nausea, vomiting, diarrhoea. Rare: pancreatitis, gallstones, cholecystitis, gastroparesis, bowel obstruction	1.4% (26 weeks)	No BMI reduction at diabetes doses; BMI reduction seen in youth obesity, not YOT2D; improved lipid profile	Second-line therapy; do not combine with DPP-4 inhibitors	Approved in T2D for adults aged ≥18 years; pregnancy category D
	Liraglutide		0.6–1.8 mg daily; SC injection		1.1% (26 weeks)			
Dual GIP/ GLP-1 receptor agonist[55]	Tirzepatide	Enhances insulin secretion, suppresses glucagon secretion and promotes satiety	2.5–10 mg weekly; SC injection	Similar to GLP-1 receptor agonists	2.28% (30 weeks)	BMI reduction 7.4% (5 mg) and 11.2% (10 mg) (30 weeks)	Second- or third-line therapy; do not combine with DPP-4 inhibitors	Approved for adults aged ≥18 years; pregnancy category D

Abbreviations: BMI = body mass index; DKA = diabetic ketoacidosis; DPP-4 = dipeptidyl peptidase-4; GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide-1; HHS = hyperosmolar hyperglycaemic state; NS = nonsignificant; SC = subcutaneous; SGLT-2 = sodium-glucose cotransporter 2; T2D = type 2 diabetes; YOT2D = youth-onset type 2 diabetes.
*Pharmacokinetic data are available for metformin, insulin, dulaglutide, empagliflozin and dapagliflozin in YOT2D. Tirzepatide dosing is based on physiologically based pharmacokinetic modelling.

(TODAY) study found that more than half of young people receiving metformin monotherapy required insulin within five years. An HbA_{1c} level of 6.3% or greater at three months predicted subsequent loss of glycaemic control across all treatment groups. With additional drug classes now available, other agents are increasingly being used to reduce the need for rescue insulin.[20,57]

Sodium-glucose cotransporter-2 inhibitors

Sodium-glucose cotransporter-2 inhibitors (SGLT-2) inhibitors, including empagliflozin and dapagliflozin, are effective in YOT2D. Empagliflozin is TGA approved for children aged 10 years and older, whereas dapagliflozin is currently TGA approved only for adults aged 18 years and older. They are administered orally once daily and combination tablets with metformin are available. Additional renal and cardiovascular benefits have been demonstrated in adults; making these agents particularly appropriate for young people with renal impairment.[14]

A meta-analysis of three randomised controlled trials in YOT2D demonstrated significant reductions in HbA_{1c} levels compared with placebo (short-term mean difference, −0.94%; 95% confidence interval [CI], −1.27 to −0.61; long-term mean difference, −0.93%; 95% CI, −1.36 to −0.49).[58] Fewer participants required rescue therapy or discontinued treatment because of a lack of efficacy. Rates of adverse and serious adverse events were similar to those observed with placebo. These findings support SGLT-2 inhibitors as an effective add-on therapy in YOT2D.[59]

Glucagon-like peptide-1 receptor agonists

Glucagon-like peptide-1 (GLP-1) receptor agonists have strong evidence for weight reduction, and their ability to increase insulin secretion, suppress glucagon secretion and enhance satiety makes them an attractive option for young people with diabetes and obesity. However, in YOT2D, daily liraglutide and weekly dulaglutide lowered HbA_{1c} levels but did not reduce BMI at the doses studied. Currently, GLP-1 receptor agonists are only TGA approved for use in adults aged 18 years and older with T2D.

Higher-dose liraglutide and semaglutide are effective treatments for adolescent obesity; however, conclusions regarding their efficacy in YOT2D remain limited because few participants with diabetes have been included in these studies. In the Semaglutide Treatment Effect in People with Obesity (STEP) TEENS trial, semaglutide 2.4 mg once weekly reduced BMI by 16.1% in adolescents with obesity. Semaglutide 2.4 mg may therefore be considered in young people with YOT2D and obesity that is refractory to lifestyle intervention.[59]

The adverse-effect profile of GLP-1 receptor agonists in YOT2D is similar to that observed in adults, with gastrointestinal symptoms being the most common adverse effects.[59]

Dual GIP/GLP-1 receptor agonist

To date, meaningful improvements in both adiposity and glycaemia in YOT2D have been demonstrated only with the dual incretin tirzepatide; however, current TGA approval in T2D is for use in adults aged 18 years and older. Tirzepatide lowers HbA_{1c} levels by 1.5 to 2.5%, depending on dose, and produces weight loss of 10 to 15%, offering substantially greater dual metabolic benefits than existing therapies for YOT2D.[55]

The long-term durability and safety of SGLT-2 inhibitors, GLP-1 receptor agonists and tirzepatide in YOT2D remain uncertain. However, extensive safety data from adults are reassuring, and these agents represent promising treatment options, either alone or in combination. Longer-term studies of incretin-based therapies are underway and are likely to further expand treatment options.

Medications not recommended in YOT2D

Sulfonylureas are currently not recommended in YOT2D because of the risk of hypoglycaemia, weight gain and potential beta-cell decline. Thiazolidinediones are not used because of the increased risk of fracture, heart failure and macular oedema reported in adults. Dipeptidyl peptidase-4 inhibitors are not efficacious in reducing HbA_{1c} in YOT2D.[60]

Summary

Understanding the complex pathophysiology of YOT2D and recognising its distinct subtypes can help clinicians develop personalised treatment plans for young people. Targeting weight loss remains central to reducing insulin resistance and may now involve the use of agents such as semaglutide or tirzepatide alongside lifestyle interventions to reduce adiposity. Expanding pharmacotherapy options, including SGLT-2 inhibitors, GLP-1 receptor agonists and the dual GIP/GLP-1 receptor agonist tirzepatide, provide meaningful improvements in glycaemic control and offer a more optimistic outlook for young people with YOT2D. Although many traditional therapies have shown limited long-term effectiveness in YOT2D, newer incretin-based therapies provide the first substantial dual benefits for both HbA_{1c} and adiposity. Cardiometabolic and renal complications commonly seen in YOT2D should be screened for and managed as part of holistic care in addition to adiposity and glycaemic management.

Building strong relationships with young people and their families, and involving them in shared decision making, can improve adherence, minimise adverse effects and optimise outcomes in this rapidly evolving therapeutic landscape. MT

References

A list of references is included in the online version of this article (https://medicinetoday.com.au/mt/2026/july/supplements/type-2-diabetes-in-youth).

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