

Treatment strategy for children and adolescents with type 2 diabetes-based on ISPAD Clinical Practice Consensus Guidelines 2022

Tatsuhiko Urakami¹

¹Department of Pediatrics and Child Health, Nihon University School of Medicine, Tokyo, Japan

Highlights

- Dietary and exercise management are essential for the treatment of type 2 diabetes in children and adolescents.
- The goal of the initial treatment should be to attain an HbA1c level of less than 7.0%.
- Pharmacological treatments may be beneficial if the control goal is not achieved. A patient-centered approach should guide the selection of appropriate antihyperglycemic drugs.

Abstract. The principles of treatment for children and adolescents with type 2 diabetes include dietary and exercise management. For dietary management, a relatively modest dietary regimen with an appropriate energy source composition is recommended. Moderate- to vigorous-intensity aerobic activity is recommended for at least 60 min/d. Family members are encouraged to modify their lifestyles. Some patients fail to improve hyperglycemia through dietary and exercise management and eventually require pharmacological treatment. If the patient is metabolically stable (HbA1c level < 8.5% [69 mmol/mol]), metformin is the first-line treatment of first choice. In a case with ketosis or HbA1c of more than 8.5% (69 mmol/mol), insulin will be required initially with once daily basal insulin (0.25–0.5 units/kg). The goal of the initial treatment is to attain an HbA1c level < 7.0% (53 mmol/mol). If the glycemic goal is not attained, the addition of a second agent should be considered. However, the use of antihyperglycemic drugs in pediatric patients is limited in most countries. Therefore, the efficacy and safety of these drugs used in adult patients, including GLP-1 receptor agonists and SGLT2 inhibitors, should be evaluated in pediatric patients worldwide.

Key words: type 2 diabetes, diet, exercise, pharmacological treatment

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Corresponding author: Tatsuhiko Urakami, M.D., Ph.D., Department of Pediatrics and Child Health, Nihon University School of Medicine, 30-1 Oyaguchi, Kami-Cho, Itabashiku, Tokyo 173-8610, Japan

E-mail: urakami.tatsuhiko@nihon-u.ac.jp



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Introduction

Racial and ethnic disproportionality exists in the incidence of children and adolescents with type 2 diabetes. A high incidence has been reported in racial and ethnic minorities, such as Native American, African-American, Hispanic, East and South Asian, and Pacific Islander populations. In contrast, Caucasian youth are known to have a low incidence (1–3). The prevalence of type 2 diabetes has been reported to be more than half in most Asian countries, that is, 90% in Hong Kong, 60% in Japan, and 50% in Taiwan (2). A recent study demonstrated that the incidence in Asian children and adolescents ranged from 0.43 to 2.63 per 100,000 youth per year. A rapid increase in incidence has been observed in China and Hong Kong (3). However, the incidence of type 2 diabetes in children and adolescents has been increasing worldwide, including Asian countries, European countries, and the United States (4–6). The overall incidence of type 2 diabetes in children and adolescents in the United States significantly increased in the 2002–2012 period (from 9.0 per 100,000 youth per year in 2002–2003 to 12.5 compared to 100,000 youth per year in 2011–2012, $p < 0.001$), particularly among children and adolescents of racial and ethnic minority groups (non-Hispanic Black, Asian or Pacific Islander, and Native American) (4). While a Japanese study showed a dramatic increase in the incidence of schoolchildren with type 2 diabetes in Tokyo from 1975–1982, however no significant increase was observed between 1983–2015 (6). Previously, it was believed that children and adolescents living Asian countries had the highest incidence of type 2 diabetes, however, in recent years, the incidence of the United States (12.5 per 100,000 youth per year) seems much higher than that in Asian countries (0.43 to 2.63 per 100,000 youth per year) (3–6).

Obesity is a major risk factor for developing type 2 diabetes. Several studies have reported that most Caucasian children with type 2 diabetes are obese or overweight (7–10). Fifteen percent of Japanese children with type 2 diabetes are non-obese (11), and half of South Asian Urban children have normal weight (12). Obesity and insulin resistance are strongly associated with the development of type 2 diabetes. Therefore, the reduction of excessive body weight through restriction of food intake, increase in physical activity, and correction of lifestyle habits are essential for the treatment of type 2 diabetes in children and adolescents. In contrast, an Australian study (13) and the SEARCH for Diabetes in Youth study in the United States (14) demonstrated that children and adolescents with early onset type 2 diabetes had higher all-cause mortality rates than the general population. Early intervention and treatment to prevent the progression of type 2 diabetes is important, even in children and adolescents with type 2 diabetes. The Clinical Practice Consensus Guidelines of the International Society for Pediatric and Adolescent Diabetes (ISPAD) is useful for diabetes care in the

pediatric population of all racial and ethnic groups worldwide. This review addresses treatment strategies for children and adolescents with type 2 diabetes, mainly cited from the ISPAD Clinical Practice Consensus Guidelines 2022: Type 2 diabetes mellitus in children and adolescents (15).

Management

The principles of treatment for children and adolescents with type 2 diabetes include dietary and exercise management. Modification of lifestyle habits and education on diet and physical activity are fundamental for all pediatric patients with type 2 diabetes (15–18). Diabetes education from the time of diagnosis should involve not only the patient, but also all family members. It is important to educate patients to continue lifestyle modification without cessation because some patients drop out of diabetes management over time. Family support is essential for behavioral changes by a medical team, including a physician, diabetes education nurse, dietician, and psychosocial counsellor (15, 16). Adolescents have more problems adhering to treatment programs than other age groups. Care providers should emphasize the importance of continuing diabetes care to prevent complications and maintain the quality of life of healthy individuals living on the same day.

Diet

Dietary management should focus on eliminating excessive body weight gain with normal linear growth, control of emotional conditions, and improvement of hyperglycemia. **Table 1** summarizes the dietary management for children and adolescents with type 2 diabetes (15). Therefore, it is necessary to educate family members on how to interpret nutritional fact labels. The goal was to emphasize healthy parenting practices associated with diet by promoting parental modeling of healthy eating habits while avoiding an overrestriction of energy intake. Modest dietary restriction is recommended, that is, caloric restriction of 5–10% of the energy requirement of age-matched healthy children and adolescents, with an appropriate composition of energy sources (16). Strict dietary restrictions impair physical development and lead to withdrawal from diabetes care. Reduction in carbohydrate and fat intake with well-balanced energy sources and the elimination of sugar-rich soft drinks and juices should be emphasized. Therefore, increased fiber intake is recommended. Patients should promote eating each meal on schedule, preferably with family members, with no other activities (television, video games, computer-related activities, studying), and minimize frequent snack consumption. However, fast-food intake is limited.

Exercise

Regular exercise can improve blood glucose

Table 1. Dietary management in children and adolescents with type 2 diabetes

Diet
<ul style="list-style-type: none">• Teaching families to interpret nutrition fact labels.• Emphasize healthy parenting practices related to diet and activity by promoting parental modeling of healthy eating habits while avoiding overly restricted food intake.• Encourage positive reinforcement of all goals achieved (i.e., no or minimal weight gain and reduction in high-calorie drinks).• Promote meals eaten on schedule in one place, preferably as a family unit, with no other activity (television, computer, studying), and minimize frequent snacking.• Maintaining food and activity logs is beneficial for raising awareness of food and activity issues and for monitoring progress.

Adapted from Reference (15).

Table 2. Exercise management in children and adolescents with type 2 diabetes

Exercise
<ul style="list-style-type: none">• Encourage youth to participate in at least 60 min of moderate-to-vigorous physical activity daily with muscle and bone strength training for at least 3 days per week.• Reduce sedentary time, including watching television, computer-related activities, texting, and video games, to less than two hours per day.• Address sedentary time spent doing schoolwork and identifying ways to incorporate physical activity.• Promote physical activity as a family event, including daily efforts to be more physically active, such as using stairs instead of elevators, walking or bicycling to school and shop, and doing housework and yard work.• Encourage positive reinforcement of all achievements and avoidance of shaming.

Adapted from Reference (15).

concentration, reduce risk factors for cardiovascular disease, contribute to weight loss, and promote wellbeing (19, 20). **Table 2** summarizes appropriate exercises for children and adolescents with type 2 diabetes (15). Patients are encouraged to participate in at least 60 min/d of moderate- to vigorous-intensity aerobic activity with muscle and bone strength training for at least 3 d/wk (15). They are also encouraged to make daily efforts to be more physically active, such as using stairs instead of elevators, walking or bicycling instead of using a car, and doing housework and yardwork. Reduction of sedentary time is strongly recommended, that is, restricting watching television, playing computer-related activities, and playing video games to less than two hours per day (21). Feelings and sustainable physical activities are recommended to support the attainment of metabolic and weight goals.

Pharmacological Treatment

Some patients fail to achieve appropriate glycemic control with dietary management and exercise alone and require pharmacological treatment to improve glycemia (15, 16). A variety of antihyperglycemic drugs are currently available for adult patients that can improve blood glucose levels, prevent acute and chronic diabetes complications, improve insulin sensitivity, and improve endogenous insulin release and glucagon and incretin physiology (15, 22). Administration of exogenous insulin is required when oral antihyperglycemic drugs cannot achieve optimal glycemic control. Since the physiology

of children and adolescents with type 2 diabetes appears to be the same as that of adults with type 2 diabetes, antihyperglycemic drugs seem to be similarly effective in pediatric patients. However, currently available drugs in pediatric patients are limited to metformin in most countries and sulfonylurea (glimepiride) in some, and insulin is generally approved for use (15). Antihyperglycemic drugs available for adult patients are shown in **Table 3** (15, 22). Some pediatric patients may benefit from the use of off-label drugs; however, evidence of their efficacy and safety in children and adolescents remains limited. Nevertheless, several clinical trials of newer antihyperglycemic drugs are ongoing in pediatric patients with type 2 diabetes.

Initial treatment

The first choice of antihyperglycemic drugs in the initial treatment of children and adolescents with type 2 diabetes includes metformin and/or insulin alone or in combination, as determined by clinical symptoms, severity of hyperglycemia, and the presence or absence of ketosis/diabetic ketoacidosis (15). For the initial assessment and treatment in those diagnosis as type 2 diabetes, β -cell associated autoantibodies should be examined. As with type 1 diabetes, patients with positivity for antibodies require insulin treatment. For patients with stable glycemia, defined as an HbA1c level of less than 8.5% (69 mmol/mol), metformin should be used at a maximum dose of 2 g/d together with a healthy lifestyle intervention (23–26). For patients

Table 3. Non-insulin antihyperglycemic drugs for the treatment of children and adolescents with type 2 diabetes

Antihyperglycemic drugs	Mechanism of Action	Benefits	Adverse effects	Names and Dosing	Special Considerations	Percent HbA1c lowering
Approved for use in youth						
Biguanide (Metformin)	<ul style="list-style-type: none"> –Acts through AMP kinase in liver, muscle, and fat. –Reduces hepatic glucose production by decreasing gluconeogenesis and by stimulating peripheral glucose uptake. 	<ul style="list-style-type: none"> –No risk of hypoglycemia in a monotherapy –Oral administration –An initial anorexic effect and may promote body weight loss and improve lipid profiles. 	<ul style="list-style-type: none"> –Gastrointestinal symptoms –Lactic acidosis (rarely reported) 	<ul style="list-style-type: none"> –Begin with 500–1,000 mg daily for 7 days. –Titrate by 500 mg every 1–2 weeks, until the maximum tolerated dose or 1,000 mg twice a day or 850 mg three times a day of the standard metformin preparation or 2,000 mg once a day of extended-release metformin. 	<ul style="list-style-type: none"> –Avoid in ketoacidosis, if eGFR < 30, cardiac or respiratory insufficiency, or receiving radiographic contrast materials. 	1–2%
Sulfonylurea (Glimepiride)	<ul style="list-style-type: none"> –Binds to receptors on the potassium / ATP channel complex causing potassium channels to close, resulting in insulin secretion. 	<ul style="list-style-type: none"> –Oral administration 	<ul style="list-style-type: none"> –Mild to severe hypoglycemia –Weight gain 	<ul style="list-style-type: none"> –1 mg taken once a day with breakfast or the first main meal of the day. –Maximum dose is 8 mg. 	<ul style="list-style-type: none"> –May accelerate the loss of β-cell function. 	1.5–2%
Glucagon-like peptide-1 (GLP-1) receptor agonist (not approved in most Asian countries)	<ul style="list-style-type: none"> –GLP-1 is secreted by L-cells in the small intestine in response to food, increasing insulin secretion proportionate to blood glucose concentrations, suppressing glucagon, prolonging gastric emptying, and promoting satiety. 	<ul style="list-style-type: none"> –No risk of hypoglycemia in a monotherapy –Weight loss –May reduce cardiovascular, renal events and mortality. 	<ul style="list-style-type: none"> –Gastrointestinal symptoms, and infrequent dizziness, headache and dyspepsia –C cell hyperplasia and risk for thyroid carcinoma in those with Multiple Endocrine Neoplasia (MEN) 	<ul style="list-style-type: none"> –Current pediatric approved formulations are given as once-daily or once-weekly SC. –Liraglutide (Victoza 0.6–1.8 mg daily SC). Start with lower doses and increase to maximum tolerated dose. –Extended release Exenatide, 2 mg once-weekly SC –Dulaglutide once weekly SC trial in children in progress (NCT02963766) 	<ul style="list-style-type: none"> –Discontinue if pancreatitis suspected. –Do not use in combination with a DPP-4 inhibitor. 	0.5–0.8%

with ketosis/diabetic ketoacidosis or an HbA1c level of > 8.5% (69 mmol/mol), insulin should be administered initially. Once daily intermediate-acting or long-acting basal insulin (initial dose 0.25–0.5 units/kg) is usually effective for improving metabolic control. There may be a risk of hypoglycemia; however, this is uncommon. Metformin should be initiated simultaneously with

insulin after acidosis is resolved. Transition to a single use of metformin, titrating the dose of metformin to 2 g per day as tolerated, can be achieved over 2–6 wk together with decreasing the insulin dose by 30–50%, with the goal of eliminating insulin treatment. The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study demonstrated that 90% of children and

Table 3. (continue)

Antihyperglycemic drugs	Mechanism of Action	Benefits	Adverse effects	Names and Dosing	Special Considerations	Percent HbA1c lowering
Medications Currently Not Approved in Youth						
Sodium-glucose co-transporter 2 (SGLT-2) inhibitor	–Inhibits renal tubular reabsorption of glucose, leading to increased urinary glucose loss, reduction in blood glucose, and body weight loss.	–No risk of hypoglycemia in a monotherapy –Oral administration –Weight loss, blood pressure reduction, improved renal function. –May reduce cardiovascular, renal events and mortality.	–Increases in prevalence of genitourinary infections. –Potential risk of euglycemic diabetic ketoacidosis	–Canagliflozin 100–300 mg/d. –Empagliflozin 10–25 mg/d. –Dapagliflozin 10 mg/d. –Ertugliflozin 15 mg/d. –Canagliflozin, trial in progress in children (NCT03170518)	–Consider discontinuing before surgical procedure to avoid potential DKA. –Risk of volume depletion	1–2%.
Thiazolidinedione (TZD)	–Binds to nuclear protein, activating γ -peroxisome proliferative activator receptor.	–Oral administration –Increases insulin sensitivity in muscle, adipose tissue and liver.	–Weight gain, anemia, fluid retention (congestive heart failure)	–Pioglitazone: 15 mg can increase to 30 mg/d.	–Avoid use in patients with cardiac dysfunction.	0.5–1.3%
Dipeptidyl-peptidase 4 (DPP-4) inhibitor	–Inhibit the enzyme that breaks down GLP-1, resulting in higher concentrations of GLP-1.	–Oral administration –Unlike GLP-1 agonists no effect on gastric emptying, satiety or weight loss.	–Upper respiratory infections, nasopharyngitis	–Sitagliptin 100 mg/d. –Alogliptin 25 mg/d. –Saxagliptin 5 mg/d. –Linagliptin 5mg/d.	–Should not be used in combination with a GLP-1 agonist.	0.5%
α -glucosidase inhibitors	–Reduces the absorption of carbohydrates in the upper small intestine by inhibiting breakdown of oligosaccharides, thereby delaying absorption in the lower small intestine.	–Oral administration –Reduce post prandial glucose rise.	–Flatulence, diarrhea, abdominal cramps	–Must be given with meals. –Acarbose 25–100 mg three times a day –Miglitol 100 mg three times a day	–Particularly successful in countries where carbohydrates make up a substantial part of the diet.	0.5–1%

Adapted from Reference (15, 22). SC, subcutaneous injection.

adolescents with type 2 diabetes could successfully wean off insulin and achieve glycemic targets with metformin monotherapy (23–26).

Subsequent treatment

The goal of the initial treatment was to achieve an HbA1c level of less than 7.0% (53 mmol/mol). In some cases, a target of less than 6.5% (48 mmol/mol) is

recommended without the occurrence of hypoglycemic events (27, 28). If the HbA1c target is not achieved and the HbA1c level is 6.5–9.0% (48–74 mmol/mol), metformin monotherapy should be continued with a maximum dose of 2 g/d within 4 mo, in addition to a second drug (25, 29). A second-choice drug should be selected based on the degree of its glucose-lowering effect, mechanism of action, pharmaceutical pricing, approval for use in youth, dosing regimen, adverse events, and influence on comorbidities and complications. A glucagon-like peptide 1 (GLP-1) receptor agonist may be recommended as a second-choice drug if the use is approved in the home country (30, 31). With a higher HbA1c value > 9.0% (75 mmol/mol), basal insulin should be started or restated. The initial dose of basal insulin is 0.25–0.5 units/kg, and the dose is titrated according to the results of blood glucose levels by self-monitoring. If the glycemic target is not achieved with a combination of metformin and basal insulin at a dose of up to 1.5 units/kg/d, the initiation of prandial insulin should be considered, with titration to an HbA1c level less than 7.0% (53 mmol/mol) or less than 6.5% (48 mmol/mol) without hypoglycemia (Fig. 1).

Use of additional antihyperglycemic drugs

Metformin is only approved for use in pediatric patients worldwide or in the majority of countries, and sulfonylureas (glimepiride) in some countries. However, other antihyperglycemic drugs may be beneficial for glycemic control and have other additional effects, even in children and adolescents with type 2 diabetes.

1) Metformin

Metformin, a biguanide, acts through adenosine monophosphate-activated protein kinase (AMP kinase)

in the liver, muscle, and fat and reduces hepatic glucose production by decreasing gluconeogenesis and stimulating peripheral glucose uptake. Metformin does not promote endogenous insulin secretion; therefore, it has little or no risk of causing hypoglycemia when used as a monotherapy. In addition, body weight either remains stable or decreases during monotherapy and plasma lipid levels may improve (32, 33). A previous study showed that the majority of pediatric patients with recent-onset type 2 diabetes achieved a target HbA1c level of less than 8.0% (63 mmol/mol), with an HbA1c level of less than 7.0% (53 mmol/mol) in 78%, and that of less than 6.0% (42 mmol/mol) in 46%, on metformin monotherapy (23). However, the TODAY study subsequently reported that participants often required additional antihyperglycemic drugs such as rosiglitazone to sustain appropriate glycemic control for a long period (24, 25). Polycystic ovary syndrome (PCOS) is a common complication in youth with type 2 diabetes (34, 35). Obese patients with PCOS show more insulin resistance and lipid abnormalities than healthy individuals with PCOS (36). Thus, metformin may improve ovulatory abnormalities in females with PCOS (34). The most common adverse events are gastrointestinal symptoms, and vitamin B12 deficiency may occur, particularly in patients with anemia on a vegetarian diet with anemia (37). Lactic acidosis is rarely observed and restricted to patients with renal, hepatic, or cardiac insufficiency.

2) Sulfonylureas (Glimepiride)

Sulfonylureas bind to receptors on the potassium/adenosine triphosphate (ATP) channel complex, causing the potassium channels to close and promote endogenous insulin secretion. Glimepiride is a new

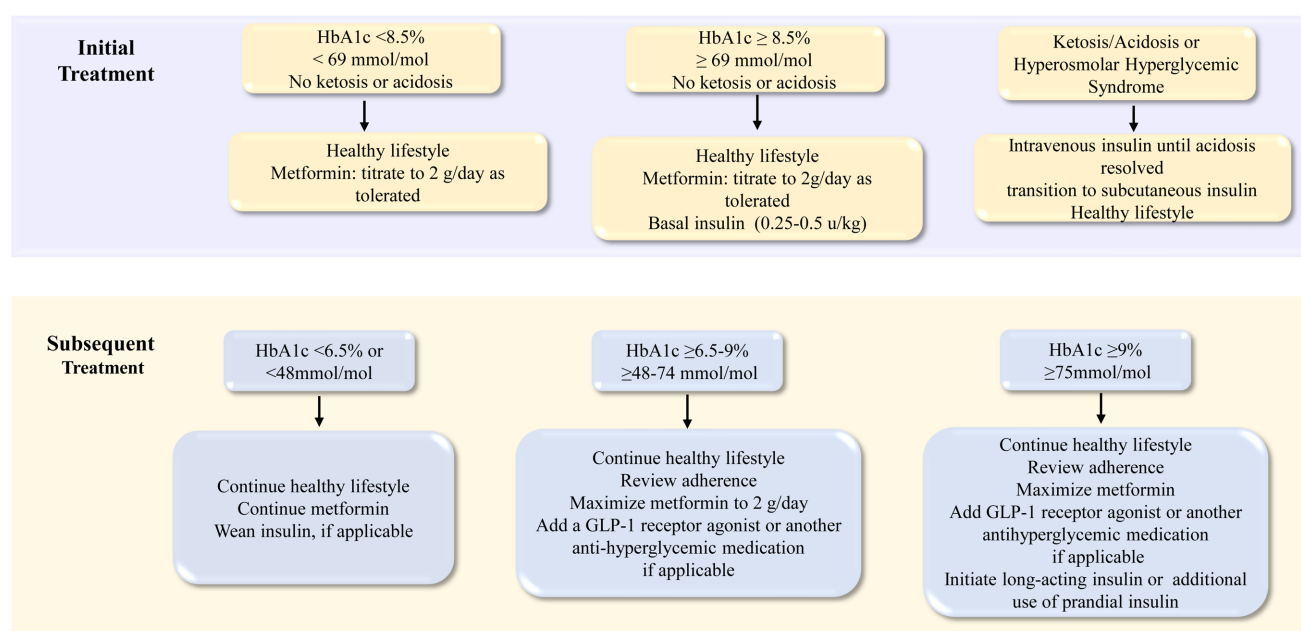


Fig. 1. Approaches to initial treatment and subsequent treatment in children and adolescents with type 2 diabetes. Adapted from Reference (15).

sulfonylurea that stimulates less insulin secretion but has additional pancreatic effects, such as decreased glucose production in the liver and enhanced insulin sensitivity in peripheral tissues (38). A single pediatric clinical trial of a sulfonylurea (glimepiride) showed a similar effect to metformin in improving glycemic control when used as monotherapy, with a greater degree of weight gain and hypoglycemia (39). Major adverse events include mild-to-severe hypoglycemia and body weight gain, and sulfonylureas may accelerate the loss of β -cell function overtime (40).

3) GLP-1 receptor agonists (not approved for use in patients aged less than 18 yr in some countries)

GLP-1 is secreted by L cells in the small intestine in response to food intake, increasing endogenous insulin secretion in proportion to blood glucose levels, suppressing glucagon release, prolonging gastric emptying, and promoting satiety (41). GLP-1 is rapidly degraded by dipeptidyl peptidase-4 (DPP-4). The Ellipse trial, a randomized double-blind clinical trial, studied the efficacy of the once-daily GLP-1 agonist liraglutide at a maximum dose of 1.8 mg per day in children and adolescents with type 2 diabetes. This trial demonstrated superiority to the placebo control in lowering HbA1c levels by 1% and 1.5% at 26 and 52 wk, respectively, and was accompanied by a small reduction in the BMI z-score [42]. Liraglutide (Victoza 0.6–1.8 mg per day) was subsequently approved by the Food and Drug Administration (FDA) for use in youth aged 12–17 yr; however, it still does not receive approval for use in some areas, including Asian countries. Recently, the long-acting GLP-1 agonist exenatide (Bydureon BCise 2 mg) was approved as a once-weekly injection for children and adolescents aged 10–17 yr based on data from the BCB114 study, which showed superiority to the placebo-control in lowering the HbA1c level, with a mean change of an HbA1c level of -0.85% from the baseline between the groups ($p = 0.012$) (31). Another weekly GLP-1 receptor agonist (dulaglutide) trial in children is currently underway (NCT02963766). GLP-1 receptor agonists are also effective in treating obesity with or without type 2 diabetes (42, 43). The use of either GLP-1 agonists or sodium-glucose co-transporter 2 (SGLT2) inhibitors is recommended as the first-choice drug in adult patients with type 2 diabetes and cardiovascular or chronic kidney disease (22, 34, 44). However, the long-term effect in cardiovascular and renal events with GLP-1 receptor agonists have not been confirmed in children or adolescents with type 2 diabetes.

4) Sodium-glucose co-transporter 2 (SGLT2) inhibitors (not approved for use in patients aged less than 18 yr)

SGLT2 inhibitors suppress the reabsorption of glucose in the proximal renal tubule, resulting in the increased excretion of urinary glucose, reduction in blood glucose, and loss of body weight. In addition, energy metabolism adapts to the relative glucose deficiency and increases lipolysis in fat cells, fatty acid oxidation, and

ketone body production in the liver during treatment with SGLT2 inhibitors (45). Hemodynamic and renal functions are profoundly modulated during treatment with SGLT2 inhibitors, which have protective effects against cardiovascular diseases and renal dysfunction (46, 47). Various studies have demonstrated a glucose-lowering effect and other additional advantages in adult patients with type 2 diabetes (22, 46, 48–50); however, its use in pediatric patients is still not approved worldwide. The use of dapagliflozin in children and adolescents with type 2 diabetes in the CANagliflozin CardioVascular Assessment Study (CANVAS) did not show superiority to metformin with or without insulin, although a sub-analysis showed a 1% reduction in HbA1c levels (51). An important adverse event associated with the use of SGLT2 inhibitors is the occurrence of diabetic ketoacidosis, particularly when used together with insulin in patients with type 1 diabetes (52–54). A systematic review and meta-analysis of 39 randomized controlled trials for adult patients with type 2 diabetes demonstrated that SGLT2 inhibitors were statistically associated with an increased risk of ketoacidosis versus control (SGLT2 inhibitors: 62/34,961 [0.18%] versus control: 23/25,211 [0.09%], with odds ratio [OR] 2.13 and 95% confidence interval [CI] 1.38 to 3.27). A possible reason for the high incidence of ketoacidosis is that SGLT2 inhibitors may fail to suppress lipolysis and ketogenesis, even if blood glucose levels are not elevated (55, 56). Decreased renal clearance of ketone bodies is another mechanism by which ketoacidosis is exacerbated.

5) Thiazolidinediones (not approved for use in patients aged less than 18 yr)

Thiazolidinediones bind to nuclear protein, activating γ -peroxisome proliferative activator receptor. They increase insulin sensitivity in the muscle, adipose tissue, and liver, and show a greater effect on glucose uptake in the liver than metformin. Adding the use of thiazolidinedione or rosiglitazone to metformin was shown to be more effective for lowering blood glucose level in the TODAY study: i.e., therapeutic failure rates in the group receiving metformin plus rosiglitazone (38.6%) versus metformin alone (51.7%), and versus metformin plus lifestyle modification (46.6%) (25). Thiazolidinediones may be useful for patients with severe insulin resistance and normal cardiac function, particularly when metformin is not tolerated. The adverse events associated with thiazolidinediones include weight gain, anemia, and fluid retention (congestive heart failure). Pioglitazone is preferable because it causes fewer cardiovascular adverse events than rosiglitazone in adult patients with type 2 diabetes (57). Liver toxicity was not observed with the newer thiazolidinediones.

6) DPP-4 inhibitors (not approved for use in patients aged less than 18 yr)

DPP-4 inhibitors suppress the breakdown of GLP-1, resulting in increased GLP-1 levels. Unlike GLP-1

agonists, these do not affect gastric emptying, satiety, or body weight. A randomized, double-blind, placebo-controlled dose-finding study of the DPP-4 inhibitor linagliptin demonstrated that both doses (1 and 5 mg) were effective in reducing HbA1c and fasting plasma glucose levels in children and adolescents with type 2 diabetes aged 10–18 yr (58). However, in another randomized clinical trial in children and adolescents with type 2 diabetes, sitagliptin did not show a beneficial effect compared with metformin monotherapy (59).

7) α -Glucosidase inhibitors (not approved for use in patients aged less than 18 yr)

α -Glucosidase inhibitors reduce the absorption of carbohydrates in the upper small intestine by suppressing breakdown of oligosaccharides, resulting in delaying absorption in the lower small intestine. They can reduce the postprandial increase in blood glucose levels and improve glycemia, particularly in patients with early stage diabetes. Combination therapy with other antihyperglycemic drugs is useful. The most common adverse events are flatulence, diarrhea, and abdominal cramps.

8) Insulin

Insulin is the oldest hyperglycemic agent used in children and adolescents with type 2 diabetes. In the 1980s, oral hyperglycemic drugs were almost completely prohibited for pediatric use, and insulin was the only hyperglycemic agent approved for use in pediatric patients. Currently, the ISPAD Clinical Practice Consensus Guidelines recommend the use of once-daily injections of intermediate- or long-acting basal insulin to support basal insulin secretion for initial and subsequent treatment in children and adolescents with type 2 diabetes. The combination treatment with GLP-1 receptor agonists and basal insulin is associated with reduced hypoglycemia and body weight loss in adults (60). In the second step of insulin treatment, administration of prandial insulin (short- or rapid-acting insulin) once to three times daily should be considered, with prandial insulin providing greater flexibility in meal planning (15). Insulin regimens should be titrated to achieve appropriate glycemic control. Patients who have completely lost endogenous insulin secretion eventually progress to intensive insulin treatment, such as multiple daily injections of insulin or insulin pump therapy, similar to that used in patients with type 1 diabetes (16).

Choice of appropriate antihyperglycemic drugs

Consensus reports from the American Diabetes Association (ADA) (22) and the European Association for the Study of Diabetes (EASD) (61) proposed that a first-choice antihyperglycemic drug for adult patients with type 2 diabetes depends on comorbidities, patient-centered treatment factors, and patient needs

and includes metformin with comprehensive lifestyle modification. A patient-centered approach should guide the selection of appropriate antihyperglycemic drugs. Efficacy, safety, adverse events, risk of hypoglycemia, impact on body weight, cost, and effects on cardiovascular and renal comorbidities. Consequently, SGLT2 inhibitors and GLP-1 receptor agonists are recommended as add-on drugs with demonstrated benefits in patients with cardiovascular and chronic renal diseases. Controversially, sulfonylureas should not be used in patients with risk factors for hypoglycemia, and metformin, sulfonylureas, and thiazolidinediones should not be used in patients with renal failure. Metformin and thiazolidinediones are contraindicated for patients with heart failure. In addition, sulfonylureas and insulin may promote obesity through noncritical use.

In contrast, most Caucasians with type 2 diabetes are obese; however, some Asian patients are not (11, 12, 62). A comparison of insulin-secretory capacity and insulin resistance between Caucasians and Japanese individuals has shown that Japanese individuals have lower insulin-secretory capacity than Caucasians, even though their glucose tolerance is normal. Caucasians display rapidly increasing insulin resistance as they progress from normal glucose tolerance to diabetes, whereas Japanese people tend to exhibit lower insulin-secretory capacity than that usually associated with increased insulin resistance (63, 64). Based on these findings, the Japan Diabetes Society (JDS) proposed that antihyperglycemic drugs in type 2 diabetes should be selected to address the diabetes pathology and background characteristics involved; the Society also proposed a different treatment strategy for Japanese from that for Caucasians (65). i.e. For obese patients with a greater contribution of insulin resistance to the pathology, metformin, SGLT2 inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors, and thiazolidinediones are recommended as first-choice drugs. α -glucosidase inhibitors are also useful for reduction of postprandial rise of blood glucose. For non-obese patients with an assumed contribution of insulin secretion failure to the pathology, insulin secretagogues, such as sulfonylureas, GLP-1 receptor agonists, and DPP-4 inhibitors, are recommended as first-choice drugs. Metformin, SGLT2 inhibitors and α -glucosidase inhibitors are also available. Non-obese patients are likely to progress to insulin treatment over time to achieve appropriate glycemic control as the β -cell function gradually declines (11).

From these points of view, **Table 4** summarizes possible pharmacological options in children and adolescents with type 2 diabetes. We propose that the present treatment should be reviewed every 2–3 mo after initiation to avoid delays in treatment intensification. Pharmacological treatment needs to be immediately adjusted for each patient who has failed to achieve the HbA1c control goals. It is also important to promote dietary management tailored to address diabetes pathology and nephropathy, as well as physical activity and lifestyle modifications in each patient (65).

Table 4. Possible pharmacological options in children and adolescents with type 2 diabetes

Recommended options for obese patients	Recommended options for non-obese patients
First-choice drug Metformin	First-choice drugs Sulfonylurea (glimepiride)
Second-choice drugs SGLT2 inhibitors GLP-1 receptor agonists DPP-4 inhibitors Thiazolidinediones	GLP-1 receptor agonists DPP-4 inhibitors Another available drugs Metformin SGLT2 inhibitors α -glucosidase inhibitors
Another available drugs α -glucosidase inhibitors	
Additional medication benefits for comorbidities	
Chronic kidney disease: SGLT2 inhibitors, GLP-1 receptor agonists	
Heart failure: SGLT2 inhibitors	
Cardiovascular disease: SGLT2 inhibitors, GLP-1 receptor agonists	
SGLT2 inhibitor, sodium-glucose co-transporter 2 inhibitor; GLP-1 receptor agonist, glucagon-like peptide-1 receptor agonist; DPP-4 inhibitor, dipeptidyl peptidase-4.	

Conclusions

Currently available antihyperglycemic drugs in adult patients with type 2 diabetes seem to be effective in controlling glycemia and, in some patients, offer beneficial effects for preventing cardiovascular and renal comorbidities without any problematic adverse events, even in pediatric patients aged > 10 yr. The efficacy and safety of these drugs in pediatric patients should be

evaluated in large-scale studies worldwide, and approval for pediatric use is expected.

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