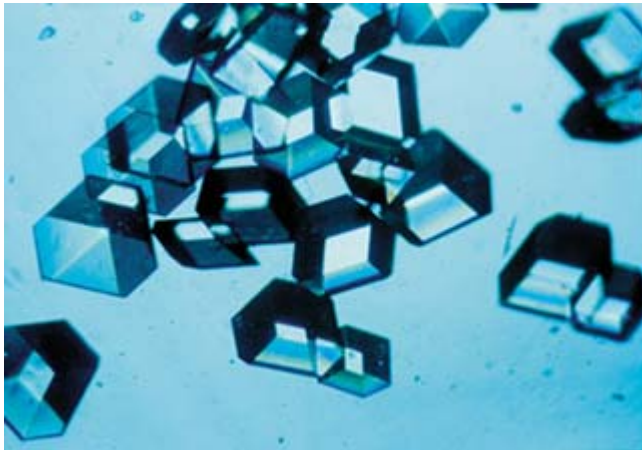


Anti-Diabetic Medication: Hypoglycemic Agents

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Type 2 diabetes is becoming more common in children due to the increasing incidence of obesity in the pediatric population. Children with type 2 diabetes usually present with obesity, symptoms suggestive of insulin resistance, and a confirmatory laboratory test of elevated random plasma glucose or fasting plasma glucose concentration or an elevated hemoglobin A1C percentage. The classical symptoms of diabetes, such as polydipsia and polyuria, are usually seen late in the presentation of type 2 diabetes in children. Metformin should be used in all children with type 2 diabetes.



Overview

Type 2 diabetes is a **multisystemic metabolic disease** that affects the vascular, renal, hepatic, nervous, and endocrinological systems and is characterized by **hyperinsulinemia, insulin resistance**, a clear correlation with **central obesity**, and **impaired glucose homeostasis**; therefore, children with type 2 diabetes are usually obese and have **dyslipidemia** and **hyperglycemia**.

Epidemiology of Type 2 Diabetes in Children

Before we dive into the different treatment options, we should review a few points concerning the epidemiology of type 2 diabetes in children.

The most recent epidemiological studies estimate the prevalence of type 2 diabetes in children **between 12 and 19 years** of age to be as high as **23%**. **African American children and other non-white ethnic groups** have a higher incidence of type 2 diabetes compared to white children.

According to a recent study, the estimated annual incidence of type 2 diabetes in white

children **younger than 20 years** of age was 3 per 100,000. The annual incidence of the disease was significantly higher in African American children at an estimated figure of 15.7 per 100,000.

An **incidence peak** was observed in children **between 15 and 19 years** of age. **Girls** seem to have a slightly higher risk of developing type 2 diabetes compared to boys.

Pathophysiology of Type 2 Diabetes

The main pathophysiological changes observed in type 2 diabetes are similar in children and adults. The **pancreatic beta-cells** show **impaired insulin secretion**, and the peripheral tissues show **reduced insulin sensitivity**. **Central obesity** and **dyslipidemia** are believed to play a crucial role in the development of insulin resistance in children and adults.

Due to the reduced insulin sensitivity in the peripheral tissues, pancreatic beta-cells try to compensate by increasing their secretion of insulin. This is believed to result in a **vicious cycle** that eventually leads to **beta-cell exhaustion** and further impairment of the function of the pancreatic beta-cells.

Clinical Presentation of Type 2 Diabetes in Children

The diagnosis of type 2 diabetes in children is difficult because severe and classical diabetic symptoms usually do not present until late stages of the disease. Children with type 2 diabetes are usually **obese**.

The characteristic symptoms of type 2 diabetes in children include **polyuria**, **polydipsia**, and **blurred vision**. In contrast to type 1 diabetes, weight loss and diabetic ketoacidosis are not common presentations of type 2 diabetes in children.

The previously mentioned symptoms are believed to be linked to the **hyperosmolar state** due to **hyperglycemia**. Symptoms of insulin resistance including **acanthosis nigricans**, **dyslipidemia**, and **elevated blood pressure**, also should be investigated in these children. Girls with signs and symptoms suggestive of type 2 diabetes and [insulin resistance](#) should be evaluated for the possibility of [polycystic ovary syndrome](#).

Diagnostic Workup for Type 2 Diabetes in Children

The diagnosis of type 2 diabetes in children can be confirmed by the presence of the classical clinical symptoms in addition to certain laboratory findings. A **random plasma glucose concentration above 200 mg/dL**, when combined with the classical symptoms of diabetes, is usually enough to confirm the diagnosis in children.

A **fasting plasma glucose concentration of more than 126 mg/dL** can also be used to confirm the diagnosis of type 2 diabetes in children regardless of the presence of the classical symptoms. An **elevated hemoglobin A1C level** of 6.5% or more is also diagnostic of type 2 diabetes in children.

Due to the delayed presentation of the classical symptoms of diabetes in children, a random plasma glucose test or a fasting plasma glucose test is recommended in any child who has a **body mass index above the 85th percentile**, especially when they have a **family history** of type 2 diabetes or when they show symptoms suggestive of **peripheral insulin resistance**.

Treatment of Type 2 Diabetes in Children

In this discussion, we will focus on the efficacy and safety of **oral hypoglycemic agents** in the management of type 2 diabetes in children. Before we discuss the different treatment options, we should emphasize the goals for the treatment of type 2 diabetes in children.

The goals of treatment are to achieve hemoglobin A1C less than 7% and fasting plasma glucose concentration between 70 and 130 mg/dL, and to prevent the microvascular and macrovascular complications of type 2 diabetes.

Non-pharmacological management of type 2 diabetes in children

Unfortunately, **lifestyle modifications** alone very rarely succeed in lowering the plasma glucose levels to the goals set for children. Regardless, children should still be encouraged to partake in **moderate to vigorous physical exercise** for several reasons.

Moderate to vigorous exercise for approximately 60 minutes per day is known to decrease peripheral insulin resistance, to help children lose weight, to improve mood, and to improve the efficacy of oral hypoglycemic agents used to treat type 2 diabetes. Additionally, moderate to vigorous exercise will lower the risk of cardiovascular disease in children.

Children also should be encouraged to eat a **healthier diet**. The intake of sugar-sweetened juices and other high-calorie beverages should be limited, while the intake of fruits and vegetables should be increased.

Oral hypoglycemic agents in children

When a child presents to the healthcare provider because of type 2 diabetes, an important decision must be made about whether to prescribe insulin. Typically, when the child is not symptomatic, hemoglobin A1C is < 9%, and random plasma glucose concentration is below 250 mg/dL, **insulin therapy** should be delayed.

Children who meet the above criteria should be started on **metformin combined with lifestyle modifications**. Metformin is very effective in lowering the random plasma glucose concentration and the hemoglobin A1C percentage and in helping children lose weight.

The maximum dose of metformin in children is **usually 2 grams per day**. This maximum dose should be reached gradually. Children with **impaired renal function** should receive a lower dosage of metformin, and renal function should be monitored closely due to the slightly increased risk of developing **lactic acidosis**.

Thiazolidinediones, such as **rosiglitazone**, are being evaluated for the treatment of type 2 diabetes in children. The efficacy of rosiglitazone is inferior compared to metformin for the management of hyperglycemia in children, and the safety of the drug is questionable. Therefore, thiazolidinediones to date have not been approved for use in the management of type 2 diabetes in children except for research purposes.

Children who do not respond to metformin alone, or who have contraindications to metformin, might benefit from the addition of a **sulfonylurea**. **Glimepiride** from 1 to 8

mg once daily and **glipizide** at 2.5 mg twice daily have been evaluated for the management of type 2 diabetes in children and found to be effective and safe.

The use of sulfonylureas in children is considered off-label according to the food and drug administration, but this use is common and acceptable in clinical practice.

While **meglitinides**, such as **repaglinide** and **nateglinide**, have been used as adjunctive therapy in the management of type 2 diabetes in adults, their use in children is not approved. **Alpha-glucosidase inhibitors**, such as **acarbose**, can be used as adjunctive therapy for the management of type 2 diabetes in children, but they are usually poorly tolerated due to the common gastrointestinal side effects, such as diarrhea and abdominal cramps.

Glucagon-like peptide-1 agonists, such as **exenatide**, are being studied in the pediatric population. Although these agents appear to be effective, they have not been approved for use in children. This group of oral hypoglycemic agents is very effective in lowering the hemoglobin A1C percentage, and we hope that they soon will be approved for the treatment of type 2 diabetes in children.

The main reason for delayed approval is the lack of randomized clinical trials in children and the possibility of poor tolerability due to common side effects, such as nausea, vomiting, headache, and diarrhea. These agents can cause hypoglycemia, which has been argued to be more hazardous to the developing brain than hyperglycemia; this point also has contributed to delays in the approval of these agents for use in children.

The amylin analog **pramlintide** is used for the management of type 1 diabetes in children. However, this agent is not approved for the management of type 2 diabetes in children due to the very high risk of severe hypoglycemia.

Fortunately, metformin with lifestyle modifications, with or without sulfonylureas, is usually sufficient for the treatment of type 2 diabetes in children.

Insulin and Type 2 Diabetes in Children

Insulins are safe and effective in the management of hyperglycemia in children. The most commonly used insulins in children are **aspart, glulisine, lispro, regular, neutral protamine Hagedorn, detemir, and glargine**.

The discussion of insulin's use in the management of type 2 diabetes in children is not covered in this article, but there are certain points that should be emphasized about when to use insulin in a child with type 2 diabetes.

Children who present with **diabetic ketoacidosis** and **thin children** with type 2 diabetes might benefit from insulin treatment without any delay. Additionally, children who present with a **random plasma glucose concentration of 250 mg/dL or more** should be started on insulin. Children who have a **hemoglobin A1C percentage of more than 9%** are better off with insulin therapy from the beginning.

The use of insulin in the management of type 2 diabetes in children is usually **temporary**. The rationale behind the temporary use of insulin is the hypothesis that use of exogenous insulin will allow the **beta-cells to rest and recover**. After an initial period of using insulin, the child can be gradually titrated down from insulin and maintained on oral hypoglycemic therapy.

References

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