Type 2 Diabetes Mellitus in Children and Adolescents

Kavitha Dileepan, MD, MPH*
M. Max Feldt, DO†

Author Disclosure
Drs Dileepan and Feldt have disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

Educational Gaps

The growing pandemic of childhood obesity has led to marked increases in the incidence and prevalence of type 2 diabetes mellitus (DM) and has further complicated the differentiation between type 2 and type 1 DM because more children with type 1 DM are overweight at time of diagnosis. In addition, numerous studies have demonstrated β-cell autoimmunity in children with type 2 DM. (1)

Objectives

After completing this article, readers should be able to:

1. **Differentiate between and understand the treatment of type 2 diabetes mellitus (DM) and type 1 DM by recognizing underlying pathophysiologic characteristics, clinical features, and laboratory markers.**
2. **Recognize the difficulty in distinguishing between type 2 and type 1 DM because of the increasing prevalence of childhood obesity.**
3. **Understand the increased prevalence of type 2 DM in children and adolescents, especially among certain racial/ethnic groups.**
4. **Recognize risk factors, appropriate screening, and diagnosis of type 2 DM, and understand the appropriate treatment for type 2 DM in the pediatric population.**
5. **Recognize the comorbidities and complications associated with type 2 DM in children and adolescents and understand that these may be present at the time of diagnosis.**

Introduction

Type 2 diabetes mellitus (DM), historically considered a serious chronic medical condition only for older individuals, now has an increased prevalence in children and adolescents. The estimated overall incidence of type 2 DM is 22 cases per 100,000 youth or approximately 3600 youth diagnosed with the condition each year. (2) From a public health perspective, DM is the seventh leading cause of death in the United States, a figure that is likely underestimated. (3) The total cost to treat DM in both adults and children is approximately $174 billion per year, and medical expenses for individuals with diagnosed DM are 2.3 times higher than for those without DM. (3) The clinical and financial burdens of DM are increased by the complications and comorbidities of the disease. Because complications of DM develop and worsen during the disease, (2) it is important to effectively recognize and manage type 2 DM early when it is diagnosed during childhood and adolescence.

Abbreviations

ADA:	American Diabetes Association
DM:	diabetes mellitus
FDA:	Food and Drug Administration
GAD:	glutamic decarboxylase
HbA1c:	hemoglobin A1c
OGTT:	oral glucose tolerance test
TODAY:	Treatment Options for Type 2 Diabetes in Adolescents and Youth

Definition

DM represents a group of endocrine disorders characterized by hyperglycemia caused by defective insulin secretion, defective insulin action, or both. (4) The original division into 2 types was based on age at presentation and dependence on insulin. Now categories of DM (Table 1) are differentiated by their known underlying pathophysiologic characteristics. All forms of DM ultimately lead to hyperglycemia, although there may be overlap in the fundamental pathologic processes in each patient.

*Department of Pediatrics, University of Missouri Kansas City School of Medicine, Children's Mercy Hospital Kansas City, MO. Dr Dileepan was a pediatric endocrinology fellow at Children's Mercy Hospital, Kansas City, MO, at the time this article was authored.
†Department of Pediatrics, University of Missouri Kansas City School of Medicine, Children's Mercy Hospital, Kansas City, MO.

Table 1. Classification of Diabetes Mellitus (DM) Causes

- Type 1 DM: β-cell destruction, typically leading to absolute deficiency in insulin secretion
  - Type 1a: immune mediated, characterized by positive circulating autoantibodies
  - Type 1b: idiopathic
- Type 2 DM: clinical spectrum from predominant insulin resistance with relative insulin deficiency to a predominant defect in insulin secretion with accompanying insulin resistance
- Gestational DM
- Other types of DM
  - Genetic defects of β-cell function (ie, monogenic diabetes of youth)
  - Genetic defects in insulin action (ie, leprechaunism, Rabson-Mendenhall syndrome, and lipoatrophic DM)
  - Diseases of exocrine pancreas or pancreatic destruction (ie, cystic fibrosis, pancreatitis, trauma, and hemochromatosis)
  - Endocrinopathies (ie, Cushing syndrome, acromegaly, glucagonoma, hyperthyroidism, and pheochromocytoma)
  - Drug induced (ie, glucocorticoids, diazoxide, β-adrenergic agonists, and asparaginase)
  - Infections (ie, cytomegalovirus and congenital rubella)
  - Other uncommon forms of immune-mediated DM (ie, stiff man syndrome and anti-insulin receptor antibodies)
  - Genetic syndromes associated with DM (ie, Down syndrome, Turner syndrome, and Klinefelter syndrome)

Epidemiology

Recent epidemiologic studies have demonstrated that more than 20% of new cases of DM in children and adolescents are due to type 2 DM. (5) The incidence of type 2 DM in children has increased in part because of the epidemic of childhood obesity and the associated insulin resistance, although the actual incidence of type 2 DM in children is likely higher than reported because of underdiagnosis.

The incidence of type 2 DM increases with age. The SEARCH for Diabetes in Youth study demonstrated that the incidence of type 2 DM in children age 10 to 19 years was 42 per 100,000 youth compared with 1 in 100,000 youth among children age 0 to 9 years. (2) The peak age at onset of type 2 DM in children coincides with pubertal timing because the mean age at diagnosis is 12 to 16 years. (6) Females have a higher incidence of type 2 DM than males, (5) likely because girls are more insulin resistant and carry more subcutaneous fat than boys. (7)

Type 2 DM disproportionately affects racial and ethnic minorities. American Indian youth have the highest incidence at 174 per 100,000. Black youth also have a particularly high incidence of 105 per 100,000 compared with 19 per 100,000 in non-Hispanic whites. (2)

Epidemiologic studies report that children born to mothers with gestational diabetes are at greater risk of developing type 2 DM. (8) Breastfeeding appears to have protective effects against the development of type 2 DM. (9)

Etiology

The cause of type 2 DM is multifactorial, but the high concordance rate among monozygotic twins (1) and the frequent association with a family history of DM (10) suggest a genetic component. Between 74% and 100% of patients with type 2 DM have a first- or second-degree relative with the disease, in contrast to only 5% of patients with type 1 DM with a family history of type 1 DM. (6) Recent studies have identified multiple genetic loci that are associated with higher risk of type 2 DM. For example, polymorphisms in the *TCF7L2* gene result in impaired insulin secretion and defective insulin processing, which confer a 1.4 times increased risk of type 2 DM. (1) More genetic markers are being identified with improvements in genetic testing.

Pathogenesis

Glucose Metabolism and Insulin Production

Glucose metabolism is tightly regulated by several processes, including sensing of glucose concentration, insulin synthesis, and secretion by pancreatic β-cells; suppression of hepatic glucose output; and insulin action on stimulated glucose uptake by the liver, intestines, and skeletal muscle. Hyperglycemia can result from derangements in any of these processes.

Typically, type 1 DM and type 2 DM are conceptualized on a spectrum. Type 1 DM results from immune-mediated destruction of β-cells, leading to insulinopenia. Type 2 DM is the result of obesity-mediated insulin resistance and non–immune-mediated deficiency in insulin secretion.

The pathogenesis of type 2 DM is complex and involves interactions between genetic and environmental factors. The core defect is varying degrees of insulin resistance and subsequent progressive insulinopenia. Other factors associated with obesity, such as elevated plasma free fatty acid concentrations and increased inflammatory markers, further inhibit β-cell insulin production and insulin-mediated glucose uptake. This leads to

a cycle of worsening hyperglycemia and further metabolic derangement.

Role of Obesity

A theory called the *accelerator hypothesis* suggests that obesity and weight gain contribute significantly to β-cell stress and confer earlier onset of all types of DM. Obesity is increasingly being accepted as a contributor to β-cell failure in genetically susceptible children, and increasing evidence suggests the influence of obesity in abnormal immune modulation. (1)

Lifestyle Contributions

During the past 30 years Americans have increased their total caloric intake by an additional 300 kcal/d. (11) Consumption of juices and sugar-sweetened beverages is a major source of these additional calories in the diet of children and adolescents (12) and is strongly associated with an increased risk of obesity and type 2 DM. (7) In addition, fewer children and adolescents are participating in recommended levels of physical activity.

In Utero Factors

The association between lower birth weight and type 2 DM suggests that in utero programming may increase the risk of type 2 DM. (13) A *thrifty-phenotype* hypothesis suggests that poor fetal nutrition produces a postnatal metabolism that is adapted to poor but not plentiful nutrition. This programming contributes to insulin resistance and can predispose the development of type 2 DM in the context of excess nutrition and obesity. (14)

Clinical Aspects

Classification of DM

Because up to 24% of children and adolescents with type 1 DM are overweight at diagnosis, (6) differentiating between type 2 DM and type 1 DM has become more difficult. (15) Further complicating the clinical delineation is the presence or absence of autoimmunity. The SEARCH for Diabetes in Youth Study measured the presence of glutamic decarboxylase (GAD) antibodies among diabetic patients. Positive GAD antibodies were found in 21% of patients with type 2 DM older than 10 years. (5) The Treatment Options for Type 2 DM in Adolescents and Youth (TODAY) study, a multicenter clinical trial, evaluated the presence of GAD and insulinoma-associated protein 2 antibodies. Of patients with diagnosed type 2 DM, 9.8% were antibody positive, 5.9% were positive for a single antibody, and 3.9% were positive for both antibodies. Those patients diagnosed as having type 2 DM who were antibody positive were more likely to be white and male and had a lower body mass index than antibody-negative patients. (16) A significant controversy exists regarding the classification of antibody-positive type 2 DM, with many authors maintaining that antibody-positive type 2 DM should be considered early type 1 DM and treated as such.

Clinical Signs and Symptoms

The presenting symptoms of type 1 and type 2 DM can be similar and include polyuria, polydipsia, and polyphagia. Weight loss can be present in both types of DM. Clinical signs to suggest type 2 DM include overweight body habitus, with more than 85% of children with type 2 DM considered overweight or obese at the time of diagnosis. (6) Acanthosis nigricans, a darkened, thick, velvety appearance to the skin found typically in folds or creases, is present in 90% of patients with type 2 DM and can be the most easily visible clinical indicator of insulin resistance. (7) The frequency of acanthosis nigricans in obese adolescents or hyperinsulinemic children varies considerably by ethnicity. Up to 90% of obese or hyperinsulinemic children in Native American populations had acanthosis nigricans, whereas it was present in less than 5% of non-Hispanic white counterparts. (7) Clinicians can look for acanthosis nigricans in the nape of the neck, axilla, groin, and over flexor surfaces. The presence of ketoacidosis, normally found in patients with type 1 DM, does not rule out type 2 DM. Some reports indicate that up to 25% of children and adolescents with type 2 DM present with diabetic ketoacidosis. (17)

Type 2 DM generally has a more insidious onset than type 1 DM, and many patients may be asymptomatic at presentation. However, because of the potentially long-standing hyperglycemia, patients may already have evidence of microvascular and macrovascular complications at the time of diagnosis. (10)

Overall, the clinical distinction between type 1 DM and type 2 DM is increasingly obscured, especially with the increasing obesity pandemic. Clinicians must weigh the evidence to support their diagnosis and consider the potential outcomes of misclassification. In the case of significant hyperglycemia, diabetic ketoacidosis, and/or positive antibodies, it may be prudent to treat patients as having type 1 DM and wean insulin therapy if the future clinical course dictates.

Diagnostic Approach

The criteria for diagnosis of DM were based on data to delineate risk for the development of retinopathy, a microvascular complication of DM, and are included in

Table 2. (10) In 2009, an international expert committee convened and added an additional criterion for diagnosis, a hemoglobin A1c (HbA1c) level greater than 6.5% (0.07). (10)

Indications to test for type 2 DM according to the Type 2 DM Consensus Panel are given in Table 3. Testing should begin at age 10 years or at the age of pubertal onset, whichever comes first, and should be repeated every 3 years. (18) The preferred method is to measure a fasting plasma glucose level, but a 2-hour plasma glucose level measured during an oral glucose tolerance test (OGTT) can be an alternative. (6)

Management

Ongoing Clinical Management

The American Diabetes Association (ADA) recommends that treatment of all children with DM should include routine follow-up every 3 months with a diabetes care team. (18) This team should include nutritional, psychological, and educational support and a medical professional experienced with DM care. The patient's self-management involves monitoring of blood glucose level, medication compliance, attention to dietary intake, and physical activity. Psychosocial considerations and medical compliance must also be addressed to ensure optimal success with therapy. The HbA1c level should be measured every 3 months during outpatient visits, and the goal HbA1c should be less than 7%. (18)(19)(20) Assessment of lipids, liver function tests, microalbuminuria, and signs and symptoms of sleep apnea should occur at diagnosis and annually. (19) Coordination between the diabetes care team and the primary care practitioner ensures a complete medical home for the child or adolescent.

Treatment should be guided by the acuity of the clinical presentation. If a patient is acutely ketotic, dehydrated, or acidotic, intravenous hydration and insulin administration with inpatient admission are warranted. If the presentation is less acute, subspecialty referral, outpatient education, and use of oral medications can be initiated. Once the patient is clinically stable, treatment of type 2 DM is dually focused on weight management and minimizing complications associated with hyperglycemia.

Table 2. Criteria to Diagnose Diabetes Mellitus

Fasting (>8 hours) blood glucose level ≥126 mg/dL (7 mmol/L)
OR
2-Hour plasma glucose level ≥200 mg/dL (11.1 mmol/L) during oral glucose tolerance test with 1.75 g/kg (maximum, 75 g/kg) of glucose
OR
Hemoglobin A1c level ≥6.5% standardized to Diabetes Control and Complications Trial assay
OR
Random plasma glucose level ≥200 mg/dL (11.1 mmol/L)
WITH
signs and symptoms of DM (ie, polyuria, polydipsia, and unintentional weight loss)

Modified by permission from American Diabetes Association. Type 2 diabetes in children and adolescents. *Diabetes Care*. 2000;23(3):381–389.

Table 3. Indications to Test for Type 2 Diabetes Mellitus (DM)

Overweight (body mass index >85th percentile, weight for height >85th percentile, or weight >120th percentile for ideal height)
WITH any 2 of the following risk factors:
Family history of type 2 DM (first- or second-degree relatives)
Race/ethnicity (American Indian, African American, Hispanic/Latino, or Asian/Pacific Islander)
Signs of insulin resistance (acanthosis nigricans)
Comorbidities of insulin resistance (hypertension, dyslipidemia, small for gestational age birthweight, cardiovascular disease, hypervirilization, steatohepatitis, and polycystic ovarian syndrome)

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Lifestyle Modification

Lifestyle modification is an essential component of the management of type 2 DM and includes an emphasis on proper diet and exercise to maintain a healthy weight while preserving linear growth. For optimal management, lifestyle modification should be centered around the family unit and not strictly on individual patients. (20)

Pharmacologic Management

Pharmacologic therapy addresses various aspects of the pathogenesis of type 2 DM (Figure) by reducing insulin resistance, increasing insulin secretion, slowing postprandial glucose absorption, or supplementing inadequate secretion of insulin. Metformin, a biguanide, is the only US Food and Drug Administration (FDA)–approved oral medication for treatment of type 2 DM in children older than 10 years and is considered first-line therapy in

nonacute presentations. The mechanism of action is to decrease hepatic glucose production and enhance insulin-mediated glucose uptake in muscle and adipose cells. Adverse effects include transient abdominal pain, diarrhea, and nausea, although it is generally well tolerated. Metformin should not be given to patients with renal insufficiency, liver disease, or cardiac or respiratory insufficiency. Patients should be warned to discontinue metformin therapy before receiving intravenous contrast for radiographic studies because of the increased risk of lactic acidosis. In adults there is evidence that metformin can normalize blood glucose levels, decrease cholesterol levels, and reduce hypertension. Metformin can also be used to normalize ovulatory abnormalities in patients with polycystic ovarian syndrome. It is available in a liquid formulation and as an extended-release formulation, which can aid compliance and potentially reduce adverse effects. The recommended starting dose for metformin is 500 mg given orally once daily, with a maximum dose of 2000 mg per day.

Insulin is used to attain early normalization of glycemic control, especially in patients who are acutely ill or have significant hyperglycemia, and insulin therapy should be started in all patients who present with diabetic ketoacidosis. Recent American Academy of Pediatrics clinical practice guidelines on the management of newly diagnosed type 2 DM recommend that insulin therapy be initiated in patients who have a random blood glucose level greater than 250 mg/dL (13.9 mmol/L) or whose HbA1c level is greater than 9%. (20) Once the diagnosis of type 2 DM is determined, insulin therapy can often be reduced as metformin therapy is initiated. Adverse effects of insulin can include weight gain from its anabolic effect on metabolism. Hypoglycemia, a potential adverse effect, is not as common among patients with type 2 DM.

Other therapies, although not FDA approved for patients younger than 18 years, can be used by the diabetes management team to improve glycemic control. Sulfonylureas (glyburide, glipizide, and glimepiride) directly increase insulin secretion, so they are most useful when there is residual β-cell function. Major adverse effects include hypoglycemia and weight gain. Glucosidase inhibitors (acarbose and miglitol) reduce absorption of carbohydrates in the upper small intestine. They can lower HbA1c levels by 0.5% to 1%, and the major adverse effects are gastrointestinal intolerance and flatulence. Incretins (exenatide) are designed to increase postprandial insulin secretion. Exenatide is administered as a twice-daily injection. Adverse effects include nausea, vomiting, diarrhea, dyspepsia, jitteriness, dizziness, headaches, and hypoglycemia, especially if given with a sulfonylurea. Thiazolidinediones (rosiglitazone and pioglitazone) increase insulin sensitivity in muscle, adipose tissue, and the liver. In isolation, they can reduce HbA1c levels by 0.5% to 1.3%. Results from the TODAY study demonstrated that metformin in combination with rosiglitazone was more successful than metformin alone or metformin with lifestyle modification in preventing an increase in HbA1c levels above 8% (0.08). (20) There is some evidence that this combination may improve lipid profiles by lowering triglyceride levels and increasing high-density lipoprotein levels. (21) Adverse effects include edema, weight gain, and anemia and may infer additional cardiac risk (Figure).

Prognosis

The risk of DM-related complications is directly related to the duration of disease. Prompt diagnosis and appropriate therapy are paramount in reducing this risk. Because of its insidious onset, many patients with type 2 DM have evidence of complications at the time of diagnosis. Among a sample of 100 Pima Indians with type 2

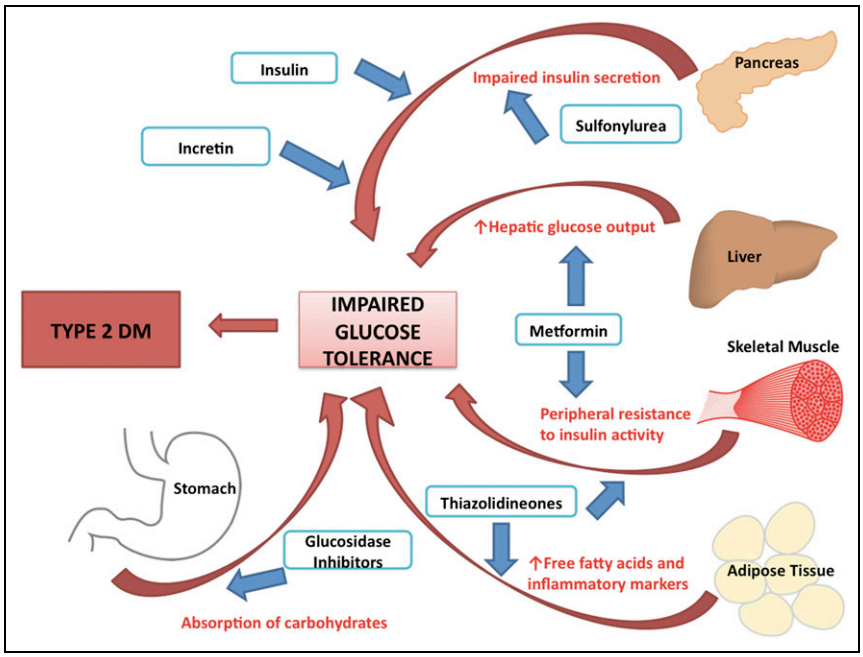

Figure. Pathogenesis and therapeutic targets. DM = diabetes mellitus.

DM, 18% had hypertension, 7% had dyslipidemia, and 22% had microalbuminuria at the time of diagnosis. (22) Microvascular complications of type 2 DM include nephropathy, retinopathy, and neuropathy. Macrovascular complications include hypertension and hyperlipidemia, which can lead to cardiovascular disease. The ADA recommends that patients with type 2 DM have blood pressure measurements performed at every routine diabetes visit. (18) In the UK Prospective Diabetes Study, hypertension was found to be a more significant predictor of cardiovascular disease than blood glucose control. This study also found a 25% reduction in the risk of microvascular complications when the average HbA1c level decreased from 7.9% to 7.0%. (23)

Patients should be screened for retinopathy with a dilated eye examination near the time of diagnosis and then yearly afterward. A lipid profile should be performed shortly after diagnosis, once glycemic control is attained, and should be performed annually thereafter. Urine microalbumin should be measured at diagnosis to assess for early nephropathy and followed up yearly. (18)

Primary public health prevention efforts should target the general population to limit the prevalence of obesity. Secondary prevention should focus on screening those children who are at high risk for the development of type 2 DM (Table 2). Tertiary prevention in patients with type 2 DM should address reduction of complications.

Summary

- On the basis of strong research evidence and consensus, type 1 diabetes mellitus (DM) remains the most common form of DM in children and adolescents. The incidence of type 2 DM in the pediatric population is rapidly increasing because of the obesity epidemic, and minority groups are disproportionately affected. (2) (10) (19)
- On the basis of some research evidence and consensus, it can be challenging to initially differentiate between type 2 DM and type 1 DM clinically because of the increased prevalence of obesity, the complex interplay of autoimmunity and obesity, and common symptoms at presentation. (1) (10) (19)
- Significant evidence and consensus support a genetic basis for the development of type 2 DM in children.
- Physicians should routinely screen at risk children older than age 10 years for DM. Screening criteria include obesity, a family history of type 2 DM, a minority racial or ethnic background, acanthosis nigricans, or other diseases associated with insulin resistance, including polycystic ovary syndrome, hypertension, or dyslipidemia. (1) (10) (18) (19)
- On the basis of consensus, diagnosis of type 2 DM can be confirmed by an elevated fasting blood glucose level greater than 126 mg/dl (7.0 mmol/L), an elevated 2-hour plasma glucose greater than 200 mg/dL (11.1 mmol/L) on an oral glucose tolerance test, an elevated random blood glucose greater than 200 mg/dL (11.1 mmol/L), or a hemoglobin A1c level greater than 6.5% with suggestive symptoms. (10)
- According to strong research evidence and consensus, once the diagnosis has been made, treatment should be based on the acuity of presentation and should focus on lifestyle modification and on normalizing hyperglycemia to minimize complications. Metformin is currently first-line treatment for type 2 DM in children and adolescents older than age 10 years who present nonacutely. (18) (19)
- Strong research evidence and consensus demonstrate that because type 2 DM has an insidious onset, microvascular and macrovascular complications can be present at the time of diagnosis. Patients should be screened for the presence of complications when the diagnosis of type 2 DM is made and in follow-up. (6) (10)

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Suggested Reading

Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics.* 2011;128(suppl 5):S213–S256

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Parent Resources From the AAP at HealthyChildren.org

- English: http://www.healthychildren.org/English/health-issues/conditions/chronic/Pages/Type-2-Diabetes-A-Manageable-Epidemic.aspx
- Spanish: http://www.healthychildren.org/spanish/health-issues/conditions/chronic/paginas/type-2-diabetes-a-manageable-epidemic.aspx
- English: http://www.healthychildren.org/English/news/Pages/AAP-Publishes-First-Guidelines-to-Manage-Type-2-Diabetes-in-Children.aspx

PIR Quiz

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1. Among the following factors, which is most likely to protect a 13-year-old patient against type 2 diabetes mellitus (DM)?
   - A. Adolescent age.
   - B. Female sex.
   - C. History of being breastfed.
   - D. Mother who had gestational diabetes.
   - E. Native American race.

2. It can be difficult to distinguish between type 1 and type 2 DM in a child who presents with ketoacidosis. Among the following, which clinical finding is most suggestive of type 2 DM?
   - A. Acanthosis nigricans.
   - B. Polydipsia.
   - C. Polyphagia.
   - D. Polyuria.
   - E. Weight loss.

3. In your management of a 7-year-old boy with type 1 DM, which of the following parameters are you likely to assess every 3 months?
   - A. Albuminuria.
   - B. Hemoglobin A1c.
   - C. Lipid profile.
   - D. Liver function tests.
   - E. Signs of sleep apnea.

4. In addition to diet and exercise, you are considering pharmacotherapy for a 15-year-old girl who has had type 2 DM for the past year. Among the following, which is the only drug approved by the US Food and Drug Administration for someone her age?
   - A. Acarbose.
   - B. Exenatide.
   - C. Glipizide.
   - D. Metformin.
   - E. Pioglitazone.

5. In a patient with newly diagnosed type 2 DM, initiation of insulin therapy is recommended if which one of the following findings is present?
   - A. Fasting blood glucose level of 140 mg/dL (7.8 mmol/L).
   - B. Hemoglobin A1c level of 8.0% (0.08).
   - C. Hemoglobin A1c level of 8.5% (0.09).
   - D. Random blood glucose level of 200 mg/dL (11.1 mmol/L).
   - E. Random blood glucose 275 mg/dL (15.3 mmol/L).

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