American Academy of Pediatrics
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TECHNICAL REPORT

Management of Type 2 Diabetes Mellitus in Children and Adolescents

abstract

FREE

OBJECTIVE: Over the last 3 decades, the prevalence of childhood obesity has increased dramatically in North America, ushering in a variety of health problems, including type 2 diabetes mellitus (T2DM), which previously was not typically seen until much later in life. This technical report describes, in detail, the procedures undertaken to develop the recommendations given in the accompanying clinical practice guideline, "Management of Type 2 Diabetes Mellitus in Children and Adolescents," and provides in-depth information about the rationale for the recommendations and the studies used to make the clinical practice guideline's recommendations.

METHODS: A primary literature search was conducted relating to the treatment of T2DM in children and adolescents, and a secondary literature search was conducted relating to the screening and treatment of T2DM's comorbidities in children and adolescents. Inclusion criteria were prospectively and unanimously agreed on by members of the committee. An article was eligible for inclusion if it addressed treatment (primary search) or 1 of 4 comorbidities (secondary search) of T2DM, was published in 1990 or later, was written in English, and included an abstract. Only primary research inquiries were considered; review articles were considered if they included primary data or opinion. The research population had to constitute children and/or adolescents with an existing diagnosis of T2DM; studies of adult patients were considered if at least 10% of the study population was younger than 35 years. All retrieved titles, abstracts, and articles were reviewed by the consulting epidemiologist.

RESULTS: Thousands of articles were retrieved and considered in both searches on the basis of the aforementioned criteria. From those, in the primary search, 199 abstracts were identified for possible inclusion, 58 of which were retained for systematic review. Five of these studies were classified as grade A studies, 1 as grade B, 20 as grade C, and 32 as grade D. Articles regarding treatment of T2DM selected for inclusion were divided into 4 major subcategories on the basis of type of treatment being discussed: (1) medical treatments (32 studies); (2) nonmedical treatments (9 studies); (3) provider behaviors (8 studies); and (4) social issues (9 studies). From the secondary search, an additional 336 abstracts relating to comorbidities were identified for possible inclusion, of which 26 were retained for systematic review. These articles included the following: 1 systematic review of literature regarding comorbidities of T2DM in adolescents; 5 expert

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KEY WORDS

childhood, clinical practice guidelines, comanagement, diabetes, management, treatment, type 2 diabetes mellitus, youth

ABBREVIATIONS

AAP—American Academy of Pediatrics
ACE—angiotensin-converting enzyme
ADA—American Diabetes Association
AHA—American Heart Association
BG—blood glucose
CAM—complementary and alternative medicine
CES-D—Center for Epidemiologic Studies Depression Scale
CVD—cardiovascular disease
HbA1c—hemoglobin A1c
LDL-C—low-density lipoprotein cholesterol
PCP—primary care provider
QDS—Quality Data Set
RCT—randomized controlled trial
T1DM—type 1 diabetes mellitus
T2DM—type 2 diabetes mellitus

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opinions presenting global recommendations not based on evidence; 5 cohort studies reporting natural history of disease and comorbidities; 3 with specific attention to comorbidity patterns in specific ethnic groups (case-control, cohort, and clinical report using adult literature); 3 reporting an association between microalbuminuria and retinopathy (2 case-control, 1 cohort); 3 reporting the prevalence of nephropathy (cohort); 1 reporting peripheral vascular disease (case series); 2 discussing retinopathy (1 case-control, 1 position statement); and 3 addressing hyperlipidemia (American Heart Association position statement on cardiovascular risks; American Diabetes Association consensus statement; case series). A breakdown of grade of recommendation shows no grade A studies, 10 grade B studies, 6 grade C studies, and 10 grade D studies. With regard to screening and treatment recommendations for comorbidities, data in children are scarce, and the available literature is conflicting. Therapeutic recommendations for hypertension, dyslipidemia, retinopathy, microalbuminuria, and depression were summarized from expert guideline documents and are presented in detail in the guideline. The references are provided, but the committee did not independently assess the supporting evidence. Screening tools are provided in the Supplemental Information. *Pediatrics* 2013;131:e648–e664

INTRODUCTION

This technical report details the procedures undertaken to develop the recommendations given in the accompanying clinical practice guideline, "Management of Type 2 Diabetes Mellitus in Children and Adolescents." What follows is a description of the process, including the committee's objectives; methods of evidence identification, retrieval, review, and analysis; and summaries of the committee's conclusions.

Statement of the Issue

Over the last 3 decades, type 2 diabetes mellitus (T2DM), a disease previously confined to adult patients, has markedly increased in prevalence among children and adolescents. Currently, in the United States, approximately 1 in 3 new cases of diabetes mellitus diagnosed in patients younger than 18 years is T2DM,[1,2] with a disproportionate representation in ethnic minorities,[3,4] especially among adolescents.[5] This trend is not limited to the United States but is occurring internationally as well.[6]

The rapid emergence of childhood T2DM poses challenges to the physician who is unequipped to treat adult diseases encountered in children. Most diabetes training and educational materials designed for pediatric patients address type 1 diabetes mellitus (T1DM) and emphasize insulin treatment and glucose monitoring, which may or may not be appropriate for children with T2DM.[7,8] Most medications used for T2DM have been tested for safety and efficacy only in individuals older than 18 years, and there is scant scientific evidence for optimal management of children with T2DM.[9,10] Extrapolation of data from adult studies to pediatric populations may not be valid because the hormonal milieu of the prepubescent and pubescent patient with T2DM can affect treatment goals and modalities in ways heretofore unencountered in adult patients.[11]

The United States has a severe shortage of pediatric endocrinologists, making access to these specialists difficult or, in some cases, impossible.[12] Vast geographic areas lack a pediatric endocrinologist: in 2011, 3 states had no pediatric endocrinologists, and 22 had fewer than 10, and the situation is unlikely to improve in the near future.[13] In 2004, the National Association of Children's Hospitals and Related Institutions performed a workforce survey and found that patients had to wait almost 9 weeks for an appointment to see an endocrinologist.[14] Because the number of patients with T1DM and T2DM has increased since then, this situation is presumably worse today. Regardless of their age, most patients in the United States who have T2DM are cared for by primary care providers (PCPs).[15] Furthermore, given the expected increases in the national and global incidence of T2DM and the near impossibility that the pediatric endocrine workforce will increase proportionately, PCPs must be prepared for and capable of managing children and adolescents who have uncomplicated T2DM.

Numerous experts have argued that the ideal care of a child with T2DM is provided through a team approach, with care shared among a pediatric endocrinologist, diabetes nurse educator, nutritionist, and behavioral specialist.[16–18] In areas of limited access to pediatric endocrinologists, however, contact with the pediatric endocrinology team might involve contact at diagnosis for initial diabetes education and intermittently thereafter; annually, with interval care by a PCP and interval communication with the pediatric endocrinology team; or at every visit, for those patients who are either doing poorly or are taking insulin.

In areas where access to subspecialists is hampered by geographic distances and/or professional shortages, care provided by local generalists who are skilled in treating children and youth with T2DM is likely to improve access to medical care. Although there are no pediatric studies evaluating this issue, the committee believes that this improved access to care might result in:

- Reduced wait times and increased timeliness of care.
- Reduced economic burden to the patient, including reduced need to travel and reduced time lost from work and/or school.
- Potentially improved patient retention. Kawahara et al[19] reported that 56.9% of patients with T2DM stopped coming to their hospital diabetes clinic appointments, most commonly because they were "too busy" to keep their appointments.

Recent advances in medical technology have the potential to ameliorate limited access to specialists. Reporting on the provision of clinical specialty diabetes care to remote locations using telemedicine, Malasanos et al[20] found that weekly telemedicine clinics were able to effectively replace quarterly face-to-face clinics after an initial face-to-face clinic visit. This more frequent contact provided by the telemedicine clinics resulted in improved hemoglobin A1c (HbA1c) concentrations, better patient satisfaction, fewer days missed from work or school, more time spent with the patient during clinic visits, and fewer subsequent hospitalizations and emergency department visits. Telemedicine is costly, however, and requires equipment to be in place at both the subspecialist's office and the remote clinic; it is, therefore, not appropriate for every practice. It is possible that a similar model of service could be provided by a generalist working locally and in close communication with a specialist.

For family physicians and others who care for adult patients, managing T2DM in children poses potential challenges. The first is that what works for adults may not work for children. Experiences and results observed in adults do not necessarily apply to children. Children (and even adolescents) are not small adults; they have a changing hormonal environment, have differences in physiology, and their growth can have effects on medication doses, toxicity, and responses.[11] As a result, generalists who are confident in caring for adults with diabetes may attempt to apply adult practice experiences to children, in whom these may not necessarily be appropriate. Kaufman cited data on various drugs' effects in children and argued that harm may occur if children with T2DM are treated like adults with T2DM.[11] The author called for treatment trials for children with T2DM, to "better define the risk-benefit ratio in children and youth, since this may differ substantially from that in the adult type 2 diabetic population." In contrast, others have noted that most adolescents with T2DM are similar to adults in terms of size and reproductive maturity and argued that, in the absence of studies specifically targeted to adolescents, treatment regimens can be extrapolated from studies of adults with T2DM; they do agree, however, that more randomized controlled trials (RCTs) are needed in the pediatric population.[1]

A second challenge is presented by the conflicting evidence regarding outcomes in patients with diabetes who are managed by generalists versus subspecialists. Some studies in adult patients indicate that generalists are capable of achieving outcomes similar to those of subspecialists. Greenfield et al[21] observed that physiologic and functional status (ie, physical, psychological, social functioning) were similar at both 2 and 4 years and mortality was similar at 7 years in adult hypertensive patients with diabetes treated in multispecialty groups versus health maintenance organization general practices. Other studies indicate that generalists may achieve outcomes similar to those of diabetes specialists, as long as they have input from subspecialists.

Indeed, unlike diseases in several other specialties, care for children with diabetes that is conducted by generalists without input from specialists may be inferior to that provided by specialists. Ziemer et al[22] used an RCT design to examine the effect of providing 5 minutes of direct feedback from an endocrinologist to a PCP every 2 weeks. Performance in the feedback group was sustained after 3 years, and performance decayed in a comparison group that received computer-generated decision support reminders, including a flow-sheet section showing previous clinical data and a recommendations section. Specialist feedback contributed independently to intensification of diabetes management. In addition, "clinical inertia" (defined as failure by providers to intensify pharmacologic therapy for hyperglycemia) was more likely in a primary care versus a diabetes clinic setting (91% vs 52%) and resulted in higher HbA1c concentrations among patients.[23]

How these observations might be applied to the child who has T2DM is not entirely clear, but they suggest that regular, direct contact between the generalist and a specialist can have a positive outcome on these patients. De Berardis et al[24] reported that, compared with adult patients with diabetes mellitus who were seen in general practice offices, patients cared for in diabetes clinics were more likely to conform with process-of-care measures, including HbA1c concentrations, blood pressure, total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels, microalbuminuria testing, and foot and eye examinations and were more likely to have adequate concentrations of total cholesterol. No differences were found in glycemic, blood pressure, or LDL-C control, however. In that same study, all process-of-care measures improved when the patient was seen by a single physician

as opposed to being seen by several different physicians. No similar studies have been performed in children, and it is therefore unknown whether similar outcomes can be achieved in the pediatric population.

A third challenge is presented by the fact that children with T2DM are overrepresented among racial and ethnic minority populations and are more likely to be living in poverty; therefore, they may face significant challenges in accessing specialists, even under the best situations.[25] Recognizing these barriers to care and patients' real-world needs, it is the committee's consensus that it is impractical to expect every patient with T2DM to be able to access a pediatric endocrinologist on a regular basis. It is also unreasonable to assume that these visits will be frequent enough to provide the level of care needed to maintain the best possible metabolic control. For this reason alone, PCPs must have a thorough knowledge of the management of T2DM, including its unique aspects related to childhood and adolescence.

The committee also believes it is the PCP's responsibility to obtain the requisite skills for such care and to communicate and work closely with a diabetes team of subspecialists whenever possible. For this reason, when treatment goals are not met, the committee encourages clinicians to consult with an expert trained in the care of children and adolescents with T2DM. When first-line therapy fails (eg, metformin), recommendations for intensifying therapy should be generally the same for pediatric and adult populations. The picture is constantly changing, however, as new drugs are being introduced, and some drugs that initially seemed to be safe exhibit adverse effects with wider use. Clinicians should, therefore, remain alert to new developments in this area. Seeking the advice of an expert can help ensure that the treatment goals are appropriately set and that clinicians benefit from cutting-edge treatment information in this rapidly changing area.

Stated Objective of the American Academy of Pediatrics

Because the PCP caring for children will likely encounter T2DM, the American Academy of Pediatrics (AAP), the Pediatric Endocrine Society, the American Academy of Family Physicians, the American Diabetes Association (ADA), and the American Dietetic Association undertook a cooperative effort to develop clinical guidelines for the treatment of T2DM in children and adolescents, for the benefit of subspecialists and generalists alike. Representatives from these groups collaborated on developing an evidence profile that served as a major source of information for the accompanying clinical practice guideline recommendations. This report, based on a review of the current medical literature covering a period from January 1, 1990, to July 1, 2009, provides a set of evidence-based guidelines for the management and treatment of T2DM in children and adolescents.

It should be noted that, because childhood T2DM is a relatively recent medical phenomenon, there is a paucity of evidence for many or most of the recommendations provided in the accompanying guideline. Committee members have made every effort to demarcate in the guideline those references that were not identified in the original literature search and are not included in this technical report. Although provided for the reader's information, these references not identified in the literature search did not affect or alter the level of evidence for specific recommendations.

Composition of the Committee

The ad hoc multidisciplinary committee was cochaired by 2 pediatric endocrinologists pre-eminent in their field and included experts in general pediatrics, family medicine, nutrition, Native American health, epidemiology, and medical informatics. All panel members reviewed the AAP Policy on Conflict of Interest and Voluntary Disclosure and declared all potential conflicts.

Definitions

- Children and adolescents: patients ≥10 and ≥18 years of age.
- Childhood T2DM*:* disease in the child who typically: is obese (BMI ≥85th to 94th percentile and >95th percentile for age and gender, respectively); has a strong family history of T2DM; has substantial residual insulin secretory capacity at diagnosis (reflected by normal or elevated insulin and C-peptide concentrations); has insidious onset of disease; demonstrates insulin resistance (including clinical evidence of polycystic ovarian syndrome or acanthosis nigricans); and lacks evidence of diabetic autoimmunity. These patients are more likely to have hypertension and dyslipidemia than those with T1DM.
- Hyperglycemia: definition as accepted by the ADA. Specifically: fasting blood glucose (BG) concentration >126 mg/dL, random or 2-hour post-Glucola (Ames Co, Elkhart, IN) BG concentration >200 mg/dL.
- Clinician: any provider within his or her scope of practice; includes medical practitioners (including physicians and physician extenders), dietitians, psychologists, and nurses.
- Comorbidities: specifically limited to cardiovascular disease (CVD), hypertension, dyslipidemias and hypercholesterolemias, atherosclerosis, peripheral neuropathy, retinopathy, and nephropathy (microvascular and macrovascular). Obesity was considered a prediabetic condition and was specifically excluded.

- Diabetes: according to the ADA criteria, defined as:
  1. HbA1c concentration ≥6.5% (test performed in an appropriately certified laboratory); or
  2. Fasting (defined as no caloric intake for at least 8 hours) plasma glucose concentration ≥126 mg/dL (7.0 mmol/L); or
  3. Two-hour plasma glucose concentration ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test (test performed as described by the World Health Organization by using a glucose load containing the equivalent of 75 g of anhydrous glucose dissolved in water); or
  4. A random plasma glucose concentration ≥200 mg/dL (11.1 mmol/L) with symptoms of hyperglycemia.

(In the absence of unequivocal hyperglycemia, criteria 1–3 should be confirmed by repeat testing.)

- Diabetic ketoacidosis: the absolute or relative insulin deficiency resulting in fat breakdown with resultant formation of β-hydroxybutyrate and accompanying acidosis. Symptoms include nausea, vomiting, Kussmaul respirations, dehydration, and altered mental status.
- Fasting BG: BG concentration obtained before the first meal of the day and after a fast of at least 8 hours.
- Glucose toxicity: the effect of high BG causing both insulin resistance and impaired β-cell production of insulin.
- Intensification: increasing frequency of BG monitoring and adjustment of the dose and type of medication to decrease BG concentrations.
- Intercurrent illnesses: febrile illnesses or associated symptoms severe enough to cause the patient to stay home from school and/or seek medical care.
- Microalbuminuria: albumin-to-creatinine ratio ≥30 mg/g creatinine but <300 mg/g creatinine.
- Moderate hyperglycemia: BG concentration of 180 to 250 mg/dL.
- Moderate to vigorous exercise: exercise that makes the individual breathe hard and perspire and which raises his or her heart rate. An easy way to define exercise intensity for patients is the "talk test": during moderate physical activity a person can talk but not sing. During vigorous activity, a person cannot talk without pausing to catch a breath.
- Obese: BMI ≥95th percentile for age and gender.
- Overweight: BMI between 85th and 94th percentile for age and gender.
- Prediabetes: Fasting plasma glucose concentration ≥100 to 125 mg/dL or 2-hour glucose concentration during an oral glucose tolerance test ≥126 mg/dL but <200 mg/dL or HbA1c of 5.7% to 6.4%.
- Severe hyperglycemia: BG concentration >250 mg/dL.
- Thiazolidinediones: oral hypoglycemic agents that exert their effect at least in part by activation of the peroxisome proliferator-activated receptor-γ.
- T1DM: diabetes secondary to autoimmune destruction of β-cells resulting in absolute (complete or near complete) insulin deficiency and requiring insulin injections for management.
- T2DM: The investigators' designation of the diagnosis was used for the purposes of the literature review. The committee acknowledges that the distinction between T1DM and T2DM in this population is not always clear-cut, and clinical judgment plays an important role. Typically, this diagnosis is made when hyperglycemia is secondary to insulin resistance accompanied by impaired β-cell function, resulting in inadequate insulin production to compensate for the degree of insulin resistance.
- Youth: used interchangeably with "adolescent" in this document.

FORMULATION AND ARTICULATION OF THE QUESTION ADDRESSED BY THE COMMITTEE

The committee first formulated explicit questions for which evidence would be queried by the epidemiologist. Specific clinical questions addressed by the committee included: (1) the effectiveness of treatment modalities for T2DM in children and adolescents; (2) the efficacy of pharmaceutical therapies for treatment of children and adolescents with T2DM; (3) appropriate recommendations for screening for comorbidities typically associated with T2DM in children and adolescents; and (4) treatment recommendations for comorbidities of T2DM in children and adolescents.

These recommendations pertain specifically to patients at least 10 but younger than 18 years of age with T2DM. Although the distinction between T1DM and T2DM in children may be difficult,[26,27] for purposes of this report, the definition of childhood T2DM includes the child who typically is overweight or obese (defined as having a BMI ≥85th to 94th percentile and >95th percentile for age and gender, respectively); has a strong family history of T2DM; has substantial residual insulin secretory capacity at diagnosis (reflected by normal or elevated insulin and C-peptide concentrations); has insidious onset of disease; demonstrates insulin resistance (including clinical evidence of polycystic ovarian syndrome or acanthosis nigricans); and lacks

evidence of diabetic autoimmunity (negative for autoantibodies typically associated with T1DM). Patients with T2DM are more likely to have hypertension and dyslipidemia than are those with T1DM.

Methods

Primary Literature Search: Treatment of T2DM

The committee unanimously agreed on the objectives of the guideline and scope of the evidence search. A primary literature search was conducted by the consulting epidemiologist, using the strategy as described in the following text.

An article was eligible for inclusion if it addressed treatment of T2DM, was published in 1990 or later, was written in English, and included an abstract. Only primary research inquiries were considered; review articles were considered if they included primary data or opinion. Children and/or adolescents with an existing diagnosis of T2DM were required to constitute the research population; studies of adult patients were considered if ≥10% of their population was younger than 35 years.

The electronic databases PubMed, Cochrane Collaboration, and Embase were searched using the following Medical Subject Headings, alone and in various combinations: diabetes, mellitus, type 2, type 1, treatment, prevention, insipidus, diet, pediatric, T2DM, T1DM, non–insulin dependent diabetes mellitus (NIDDM), metformin, lifestyle, RCT, meta-analysis, child, adolescent, therapeutics, control, adult, obese, gestational, polycystic ovary syndrome, metabolic syndrome, cardiovascular, dyslipidemia, men, and women. In addition, the Boolean operators NOT, AND, and OR were used with the aforementioned terms, also in various combinations. Search limits included clinical trial, meta-analysis, randomized controlled trial, review, child: 6–12 years, and adolescent: 13–18 years.

Reference lists of identified articles were searched for additional studies using the same criteria for inclusion enumerated earlier. Finally, articles personally known to members of the committee that were not identified by other means were submitted for consideration and were included if they fulfilled the inclusion criteria.

A total of 196 articles were identified by using these search criteria. Of those, 58 were accepted as evidence for the guideline, and 138 were rejected as not meeting all requirements. A summary evidence table for the accepted articles can be found in Supplemental Information A.

Secondary Literature Search: Comorbidities of T2DM

After completion of the primary literature review, at the request of the committee, a second literature review was conducted to identify evidence relating to screening, diagnosis, and treatment of comorbidities of T2DM in children and adolescents. Similar to inclusion criteria for the primary review, an article relating to comorbidities was eligible for inclusion if it was published in 1990 or later, was written in English, and included an abstract. Again, only primary research inquiries were considered; review articles were considered if they included primary data or opinion. Children and/or adolescents in whom either T1DM or T2DM was diagnosed were required to constitute the research population; studies of adult patients were considered if ≥10% of the population was younger than 35 years. The focus of the research article must be hyperlipidemia, microalbuminuria, retinopathy, or "comorbidities of diabetes mellitus."

The electronic databases PubMed, Cochrane Collaboration, and Embase were searched using the following Medical Subject Headings, alone and in various combinations: diabetes, mellitus, type 2, type 1, pediatric, T2DM, T1DM, NIDDM, hyperlipidemia, retinopathy, microalbuminuria, comorbidities, screening, RCT, meta-analysis, child, and adolescent. In addition, the Boolean operators NOT, AND, and OR were used with the aforementioned terms, also in various combinations. Search limitations included clinical trial, meta-analysis, randomized controlled trial, review, child: 6–12 years, and adolescent: 13–18 years. Reference lists of identified articles were searched for additional studies, with the use of the same criteria for inclusion enumerated earlier. Finally, articles personally known to members of the committee that were not identified by other means were submitted for consideration and were included if they fulfilled the inclusion criteria.

A total of 75 articles were identified by using these search criteria. Of those, 26 were accepted as evidence for the guideline, and 49 were rejected as not meeting all requirements. A summary evidence table for the accepted comorbidity articles can be found in Supplemental Information B.

Analysis of Available Evidence

A strict evidence-based approach was used to extract data used to develop the recommendations presented in the accompanying clinical practice guideline. Individual articles meeting the prospective search criteria were critically appraised for strength of methodology, and they were assigned an evidence level grade on the basis of guidelines published by the University of Oxford's Centre for Evidence-based Medicine, which are synthesized in the next discussion.[28]

Levels of Evidence (Based on Methodology)

- Level 1A: Systematic review with homogeneity of included RCTs.

- Level 1B: Individual RCT with narrow CI and >80% follow-up.
- Level 2A: Systematic review with homogeneity of cohort studies.
- Level 2B: Individual cohort study, follow-up of untreated controls in an RCT, or low-quality RCT (ie, less than 80% follow-up).
- Level 2C: "Outcomes research."
- Level 3A: Systematic review with homogeneity of case-control studies.
- Level 3B: Individual case-control studies.
- Level 4: Case series; poor-quality cohort and/or case-control studies.
- Level 5: Expert opinion without explicit critical appraisal or based on physiology, bench research, or "first principles."

Grades of Evidence Supporting the Recommendations

The AAP policy statement, "Classifying Recommendations for Clinical Practice Guidelines," was followed in designating grades of recommendation (Fig 1, Table 1), based on the levels of available evidence. AAP policy stipulates that the evidence in support of each key action statement be prospectively identified, appraised, and summarized and that an explicit link between level of evidence and grade of recommendation be defined.

Possible grades of recommendations range from A to D, with A being the highest. Some qualification of the grade is further allowed on the basis of subtle characteristics of the level of supporting evidence. The AAP policy statement is consistent with the grading recommendations advanced by the University of Oxford's Centre for Evidence-based Medicine. The AAP policy statement "Classifying Recommendations for Clinical Practice Guidelines" offers further details.[29]

- Grade A: Consistent level 1 studies. (Examples include meta-analyses with appropriate adjustments for heterogeneity, well-designed RCTs, or high-quality diagnostic studies on relevant populations.)
- Grade B: Consistent level 2 or level 3 studies or extrapolations from level 1 studies. (Examples include RCTs or diagnostic studies with methodologic flaws or performed in less relevant populations; consistent and persuasive evidence from well-designed observational trials.)
- Grade C: Level 4 studies or extrapolations from level 2 or level 3 studies. (Examples include poor-quality observational studies, including case-control and cohort design methodologies, as well as case series.)
- Grade D: Level 5 evidence, or troublingly inconsistent or inconclusive studies of any level. (Examples include case reports, expert opinion, reasoning from first principles, or methodologically troubling studies with questionable validity.)
- Level X: Not an explicit level of evidence as outlined by the Centre for Evidence-based Medicine. Reserved for interventions that are unethical or impossible to test in a controlled or scientific fashion, in which the preponderance of benefit or harm is overwhelming, precluding rigorous investigation.

The relationship between grades of evidence supporting recommendations and recommended key action statements is depicted in Fig 1. Note that any given recommended key action statement may only be as strong as its supporting evidence will allow.

Recommended Key Action Statements

After considering the available levels of evidence and grades of recommendations, the committee formulated

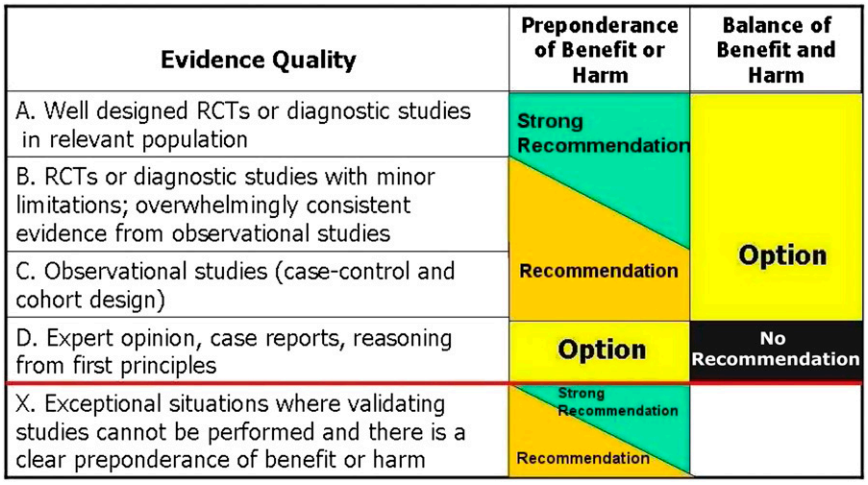

FIGURE 1

Evidence quality. Integrating evidence quality appraisal with an assessment of the anticipated balance between benefits and harms if a policy is carried out leads to designation of a policy as a strong recommendation, recommendation, option, or no recommendation.

TABLE 1 Grades of Study According to Subdivision

Evidence Quality	Medical Treatment	Nonmedical Treatment	Provider Behaviors	Social Issues
A	4	1	0	0
B	0	1	0	0
C	4	3	7	6
D	24	4	1	3

several recommended key action statements, published in the companion clinical practice guideline. As discussed previously, recommended key action statements vary in strength on the basis of the quality of the supporting evidence.

- Strong recommendation: The highest level of recommendation, this category is reserved for recommendations supported by grade A or grade B evidence demonstrating a preponderance of benefit or harm. Interventions based on level X evidence may also be categorized as strong on the basis of their risk/benefit profile. A strong recommendation in favor of a particular action is made when the anticipated benefits of the recommended intervention clearly exceed the harms (as a strong recommendation against an action is made when the anticipated harms clearly exceed the benefits) and the quality of the supporting evidence is excellent. In some clearly identified circumstances, strong recommendations may be made when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms. The implication for clinicians is that they should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
- Recommendation: A recommended key action statement is made when the anticipated benefit exceeds the harms but the evidence is not as methodologically sound. Recommended key action statements must be supported by grade B or grade C evidence; level X evidence may also result in a recommendation depending on risk/benefit considerations. A recommendation in favor of a particular action is made when the anticipated benefits exceed the harms, but the quality of evidence is not as strong. Again, in some clearly identified circumstances, recommendations may be made when high-quality evidence is impossible to obtain but the anticipated benefits outweigh the harms. The implication for clinicians is that they would be prudent to follow a recommendation but should remain alert to new information and sensitive to patient preferences.
- Option: Option statements are offered when the available evidence is grade D or the anticipated benefit is balanced with the potential harm. Options define courses that may be taken when either the quality of evidence is suspect or carefully performed studies have shown little clear advantage to 1 approach over another. The implication for clinicians is that they should consider the option in their decision-making, and patient preference may have a substantial role.
- No recommendation: When published evidence is lacking, and/or what little evidence is available demonstrates an equivocal risk/benefit profile, no recommended key action can be offered. No recommendation indicates that there is a lack of pertinent published evidence and that the anticipated balance of benefits and harms is presently unclear. The implication for clinicians is that they should be alert to new published evidence that clarifies the balance of benefit versus harm.

Implementation Strategy

Implementing the guideline's recommendations to improve care processes involves identifying potential barriers to the use of the knowledge, creating strategies to address those barriers, and selecting appropriate quality improvement methods (eg, education, audit and feedback, computer-based decision support).

Computer-mediated decision support offers an implementation mode that has been demonstrated to be effective[30] and that is expected to be of increasing relevance to pediatricians with the adoption of electronic health records. To facilitate translation of the recommendations into computable statements, the guideline recommendations were transformed into declarative production rule (eg, IF-THEN) statements.[31] The Key Action Statements are displayed as production rules in Supplemental Information C. The concepts required to describe antecedent and consequent clauses in these rules were translated into the following standardized coding systems: SNOMED-CT,[32] RxNorm,[33] and LOINC.[34]

In addition, the concepts described in the guideline recommendations were translated, where possible, into elements of the National Quality Forum's Quality Data Set (QDS).[35] The QDS provides a framework from which performance measurement data can be derived. The QDS is intended to serve as a standard set of reusable data elements that can be used to promote quality measurement. Each QDS element includes a name, a quality data type that describes part of the clinical care process, quality data type specific attributes, a standard code set name, and a code listing. The Methods for Developing the Guidelines section displays the relevant decision variables and actions as well as coding information. A QDS listing of decision variables and actions is provided in Supplemental Information D.

RESULTS

Primary Literature Search: Treatment of T2DM

Thousands of articles were retrieved and considered on the basis of the aforementioned criteria. From those,

199 abstracts were identified for possible inclusion, and 58 were retained for systematic review. Results of the literature review are presented in the following text and listed in the evidence tables in the Supplemental Information.

Of the 58 articles retained for systematic review, 5 studies were classified as grade A studies, 1 as grade B, 20 as grade C, and 32 as grade D. Articles regarding the treatment of T2DM selected for inclusion were divided into 4 major subcategories on the basis of type of treatment being discussed: (1) medical treatments (32 studies); (2) nonmedical treatments (9 studies); (3) provider behaviors (8 studies); and (4) social issues (9 studies). Detailed information about these articles is presented in Supplemental Information A. A graphic depiction of the grades of study according to subdivision is given in Table 1.

Rejected Articles

Of the 257 articles meeting search criteria, 199 were rejected, categorized as follows:

- Comorbidities: 69 studies. (Note: these articles were rejected within the context of the primary search string relating to treatment of T2DM. A second prospective literature search was conducted solely addressing comorbidities, the results of which are presented in the next section.)
- Medical treatment: 99 articles.
- Nonmedical treatment: 16 articles.
- Social issues: 12 articles.
- Provider behaviors: 3 articles.

To view the recommendations related to management of T2DM, please see the accompanying clinical practice guideline.[36]

Secondary Literature Search: Comorbidities of T2DM

Evidence is sparse in children and adolescents regarding the risks for developing various comorbidities of diabetes that are well recognized in adult patients. Numerous reports have documented the occurrence of comorbidities in adolescents with T2DM, but no randomized clinical trials have examined the progression and treatment of comorbidities in youth with T2DM.[29] The evidence that does exist is contradictory with regard to both screening and treatment recommendations. After applying the previously described search criteria and screening to thousands of articles, an additional 336 abstracts relating to comorbidities were identified for possible inclusion, of which 26 were retained for systematic review. Results of this subsequent literature review are presented in Supplemental Information E.

Articles discussing comorbidities ran the gamut of study focus, type, level of evidence, and grade of recommendation. The 26 articles that met the revised objective criteria had the following characteristics:

- Expert opinion global recommendations not based on evidence (5 articles).
- Cohort studies reporting natural history of disease and comorbidities (5 articles).
- Specific attention to comorbidity patterns in specific ethnic groups (case-control, cohort, and clinical report by using adult literature: 3 articles).
- Association between microalbuminuria and retinopathy (2 case-control, 1 cohort: 3 articles).
- Prevalence of nephropathy (cohort: 3 articles).
- Hyperlipidemia (American Heart Association [AHA] position statement on cardiovascular risks, ADA consensus statement, case series: 3 articles).
- Retinopathy (1 case-control, 1 position statement: 2 articles).
- Peripheral vascular disease (case series: 1 article).
- Systematic review of literature regarding comorbidities of T2DM in adolescents (1 article).

A graphic depiction of the grades of recommendation is given in Table 2.

Rejected Articles

A total of 310 articles did not meet primary inclusion criteria and were rejected; details are presented in Supplemental Information F. Profiles of the rejected articles are:

- Articles relating to T1DM (125 articles); specifically on the following topics:
  - Retinopathy (42 articles).
  - Vascular complications (34 articles).
  - Nephropathy (29 articles).
  - Natural history and epidemiology of T1DM (8 articles).
  - Hyperlipidemia (5 articles).
  - Risk factors for comorbidities (ie, ethnicity, puberty: 4 articles).
  - Neuropathy (3 articles).
- Articles involving adults, practice management issues, and other nonpertinent topics (118 articles).
- Articles about nondiabetic subjects, prediabetic subjects, or adults, including recommendations for testing for conditions such as hyperlipidemias and CVD (36 articles).
- Reviews, published trials, guidelines, and position statements not meeting criteria (19 articles).
- Studies addressing methods of testing for comorbidities (12 articles).

The initial search strategy for comorbidities included patients diagnosed with T1DM. The committee thus assumed that (with the exception of initiating screening) the pattern of comorbidities—and the need to screen for and treat them—would be similar between T1DM and T2DM. It was also

assumed that comorbidities would be similar between pediatric and adult patients, with length and severity of disease the driving factors. During the search, articles addressing the following themes were identified and reviewed:

- The pattern of comorbidities in T1DM versus T2DM and the role of puberty (9 articles).
- Differences in comorbidity patterns in children with T2DM compared with adults (8 articles).

Although not included in the final list of studies, these articles are included in the Supplemental Information because they resulted in an alteration to the original inclusion criteria. The results of these articles indicate that the pattern of comorbidities in children and adolescents with T2DM may not resemble that of either T1DM patients (possibly because of the influence of puberty) or adults, as was hypothesized by the committee when identifying the primary search parameters. Accordingly, the search string was modified to include only children and adolescents with the diagnosis of T2DM.

Recommendations Regarding Comorbidities

Unlike T2DM in adult patients, data are scarce in children and adolescents regarding the diagnosis, natural history, progression, screening recommendations, and treatment recommendations. Numerous reports have documented the occurrence of comorbidities in adolescents with T2DM, but no RCTs have examined the progression and treatment of comorbidities in youth with T2DM.

TABLE 2 Grades of Recommendation

Evidence Quality	No. of Studies
A	0
B	10
C	6
D	10

The available literature is conflicting regarding whether clinical signs of pathology in adults are variants of normal for adolescents, the role of puberty in diagnosis and progression of various comorbidities, the screening tests that should be performed and how they should be interpreted, when screenings should be initiated, how often screening should be performed and by whom, and how abnormal results should be treated. Medications commonly prescribed in adult patients have not been rigorously tested in children or adolescents for safety or efficacy. The peculiarities of the developing adolescent brain, typical lifestyle, and social issues confound issues of treatment effectiveness.

Despite the limited evidence available, the committee provides information on expert recommendations for the following selected comorbidities: hypertension, dyslipidemia, retinopathy, microalbuminuria, and depression. These therapeutic recommendations were summarized from expert guideline documents and are presented in detail in the following sections. The references are provided, but the committee did not independently assess the supporting evidence. Sample screening tools are provided in the Supplemental Information (see Supplemental Information H and I).

Hypertension

Hypertension is a significant comorbidity associated with endothelial dysfunction, vessel stiffness, and increased risk of future CVD and chronic kidney disease for the child with diabetes.[37,38] It is present in 36% of youth with T2DM within 1.3 years of diagnosis[39] and was present in 65% of youth with T2DM enrolled in the SEARCH for Diabetes in Youth Study (SEARCH study).[40] Because development of CVD is associated with hypertension, recognition and treatment of this comorbidity are essential, especially in youth with T2DM. Unfortunately, health care providers underdiagnose hypertension in children and adolescents (both with and without diabetes), resulting in a lack of appropriate treatment.[41]

Screening:

- Blood pressure should be measured with an appropriate-sized cuff and reliable equipment, monitored at every clinic visit, and plotted against norms for age, gender, and height provided in tables available at the following Web site: http://www.nhlbi.nih.gov/guidelines/hypertension/child_tbl.htm[42] or in "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents."[43] (See the Supplemental Information for the National Institutes of Health table.)

Treatment:

- Once a diagnosis of hypertension is established, the clinician can institute appropriate treatment, which might include lifestyle change and/or pharmacologic agents. Although a complete discussion of this topic is beyond the scope of these guidelines, rational treatment guidelines exist.[43,44] In adult patients with T2DM, concomitant treatment of hypertension has been shown to improve microvascular and macrovascular outcomes at least as much as control of BG concentrations.[45,46] Therefore, it is the consensus of this committee that similar benefits are likely with early recognition and treatment of hypertension in the child or adolescent with increased CVD risk secondary to T2DM.[47,48] The committee recommends appropriate surveillance and therapy as outlined in "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents."[43]

- Initial treatment of blood pressure consistently at, or above, the 95th percentile on at least 3 occasions should consist of efforts at weight loss reduction, limitation of dietary salt, and increased activity.
- If, after 6 months, blood pressure is still above the 95th percentile for age, gender, and height, initiation of an angiotensin-converting enzyme (ACE) inhibitor should be considered to achieve blood pressure values that are less than the 90th percentile.
- If ACE inhibitors are not tolerated because of adverse effects (most commonly cough), an angiotensin receptor blocker should be used.
- If adequate control of hypertension is not achieved, referral to a physician specialist trained in the treatment of hypertension in youth is recommended.

Dyslipidemia

Long-term complications of T2DM in children and adolescents are not as well documented as those found in adults. It should be noted that the pediatric experience with niacin and fibrates is limited. In a review, however, Pinhas-Hamiel and Zeitler[49] noted the presence of dyslipidemia in a substantial proportion of young patients with T2DM in various populations worldwide. The SEARCH study found that 60% to 65% of 2096 youth with T2DM had hypertriglyceridemia, and 73% had a low high-density lipoprotein cholesterol level.[50] Thus, although variations exist in the criteria used for defining hyperlipidemia, there is unequivocal evidence that screening for dyslipidemia is imperative in pediatric patients with T2DM.[49,51,52] Hyperglycemia and insulin resistance may play a direct role in dyslipidemia, and cardiovascular risk is further enhanced by the presence of other risk factors, including obesity and a family history of early CVD.[49,53] The AHA classifies T2DM as a tier 2 condition (moderate risk) in which accelerated atherosclerosis has been documented in patients younger than 30 years.[51] The presence of 2 other risk factors, including obesity, smoking, family history of CVD, and poor exercise history, can accelerate this status to tier 1 (high risk), which is relevant to many young patients with T2DM.

Screening:

- On the basis of current recommendations by the ADA and the AHA, at the initial evaluation, all patients with T2DM should have baseline lipid screening (after initial glycemic control has been established) consisting of a complete fasting lipid profile, with follow-up testing based on the findings or every 2 years thereafter, if initial results are normal.[51–53] (See the Supplemental Information for screening tools.)

Treatment:

The committee suggests following the AHA position statement, "Cardiovascular Risk Reduction in High-risk Pediatric Patients," for management of dyslipidemia.[51] This position statement recommends:

- Evaluation and dietary education by a registered dietitian for all patients, with initiation of intensive therapy and follow-up for patients with a BMI >95th percentile.
- Lipid targets:
  - LDL-C: Initial concentration ≥130 mg/dL: nutritionist training with diet <30% calories from fat, <7% calories from saturated fat, cholesterol intake <200 mg/day, and avoidance of trans fats. LDL measurements should be repeated after 6 months. If concentrations are still 130 to 160 mg/dL, statin therapy should be initiated, with a goal of <130 mg/dL and an ideal target of <100 mg/dL.
  - Triglycerides: If initial concentrations are between 150 and 600 mg/dL, patients should decrease intake of simple carbohydrates and fat, with weight loss management for those who are overweight. If levels are >700 to 1000 mg/dL at initial or follow-up visit, fibrate or niacin should be considered if the patient is older than 10 years because of increased risk of pancreatitis at these concentrations.
- Control of hypertension, per guidelines referenced previously.
- Intensification of management of hyperglycemia.
- Assessment of parental smoking history and patient smoking history if the patient is older than 10 years; active antismoking counseling at every visit and referral to a smoking cessation program, if required.
- Assessment of family history of early CVD along with current family lifestyle habits; a positive family history increases the level of risk.
- Promotion of physical exercise and limitation of sedentary activities.

Retinopathy

The eye has been called a unique window into the neural and vascular health in patients with diabetes.[54] Retinopathy is well documented in adults, both alone and in association with other comorbidities,[55] but descriptions of its frequency and associations with other comorbidities in youth are limited. Some observational and case-control studies show that retinopathy in adolescents with T2DM is present earlier than in adults, whereas others indicate that it appears much later.[56–60]

The review by Pinhas-Hamiel and Zeitler[49] of complications of T2DM among

adolescents cited studies in which the diagnosis of retinopathy appeared to occur strikingly early in the disease process. Two large studies in the Japanese population documented early development of retinopathy in young adults, some even before the diagnosis of diabetes mellitus. In a study of 1065 patients diagnosed with T2DM before 30 years of age, Okudaira et al[57] reported the presence of retinopathy in 99 patients (9.3%) before the first visit. One hundred thirty-five patients (12.7%) developed proliferative retinopathy before 35 years of age, and 32 (23.7%) of these patients were blind by a mean age of 32 years. Bronson-Castain et al[54] used sophisticated techniques to evaluate the neural and vascular health of the retina and reported a much higher incidence of focal retinal neuropathy, retinal thinning, and retinal venular dilation in a cohort of 15 adolescent patients with T2DM matched with 26 controls. Okudaira et al observed the development of retinopathy in 394 patients diagnosed with T2DM before 30 years of age. Of the 322 patients who were free of retinopathy at entry, 88 developed background diabetic retinopathy over 5.7 years, an incidence of 57.7 per 1000 person-years. Fifty of the 160 patients with background retinopathy developed proliferative retinopathy over 7.1 years, an incidence of 17.9 per 1000 person-years. Poor glycemic control, duration of disease, and high blood pressure seemed to be the primary risk factors.

Conversely, the study by Krakoff et al[58] of 178 youth that used the proportional hazards model showed a lower risk for retinopathy in Pima Indians (compared with the Japanese study cited previously), even after adjusting for glucose concentrations and blood pressure. Similar results were reported by Farah et al[59] in 40 African American and Hispanic youth and by Karabouta et al[60] in 7 adolescent patients. It is unclear whether these differences in results arise from variations in study design, population demographic characteristics, and/or techniques used in diagnosis. Given the variability in the results of epidemiologic studies and absence of long-term data, the committee considers it prudent for providers to follow the ADA "Standards of Medical Care in Diabetes" for identification and management of retinopathy in adolescents with T2DM, as follows[61]:

Screening:

- Patients with T2DM should have an initial dilated and comprehensive eye examination performed by an ophthalmologist or optometrist shortly after diabetes diagnosis.
- Subsequent examinations by an ophthalmologist should be repeated annually. Less frequent examinations may be considered (eg, every 2–3 years) after 1 or more normal eye examinations. More frequent examinations are required if retinopathy is progressing.

Treatment:

- Providers should promptly refer patients with any level of macular edema, severe nonproliferative diabetic retinopathy, or any proliferative diabetic retinopathy to an ophthalmologist who is knowledgeable and experienced in the management and treatment of diabetic retinopathy.
- Laser photocoagulation therapy is indicated to reduce the risk of vision loss in patients with high-risk proliferative diabetic retinopathy, clinically significant macular edema, and some cases of severe nonproliferative diabetic retinopathy.

Microalbuminuria

Microalbuminuria is a marker of vascular inflammation and a sign of early nephropathy; it has been found to be associated with CVD risk in adults. It may be present at diagnosis in youth with T2DM.[49] Higher rates of microalbuminuria have been reported among youth with T2DM than in their peers with T1DM.[39,59] Diabetic nephropathy may also be more frequent and severe among youth with T2DM.[62,63]

According to the ADA statement "Care of Children and Adolescents with Type 1 Diabetes," the definition of microalbuminuria is either:

- "Albumin-to-creatinine ratio 30–299 mg/g in a spot urine sample; slightly higher values can be used in females because of the difference in creatinine excretion,"[7,64] or
- "Timed overnight or 24-hour collections: albumin excretion rate of 20–199 mcg/min."[7]

According to the ADA, "an abnormal value should be repeated as exercise, smoking, and menstruation can affect results and albumin excretion can vary from day to day. The diagnosis of persistent abnormal microalbumin excretion requires documentation of two of three consecutive abnormal values obtained on different days."[7,65] In addition, nondiabetes-related causes of renal disease should be excluded; consultation with specialists trained in the care of children with renal diseases should be considered as required. It should be noted that orthostatic proteinuria is not uncommon in adolescents and usually is considered benign. For that reason, all patients with documented microalbuminuria should have a first morning void immediately on arising to determine if this is the case. Orthostatic proteinuria does not require treatment with medication.

The committee considers it prudent for providers to follow the ADA "Standards of Medical Care in Diabetes" for the identification and management of

microalbuminuria in adolescents with T2DM, as described here. Note that monitoring should always be done on a first morning void specimen:

Screening:

- Screening for microalbuminuria should begin at the time of T2DM diagnosis and be repeated annually.
- An annual random spot urine sample for microalbumin-to-creatinine ratio is recommended.[66]

Treatment:

- Treatment with an ACE inhibitor should be initiated in nonpregnant individuals with confirmed persistent microalbuminuria from 2 additional urine specimens, even if blood pressure is not elevated.
- If possible, treatment with an ACE inhibitor should be titrated to normalization of microalbumin excretion. "Microalbumin excretion should be monitored at three- to six-month intervals to assess both the patient's response to therapy and the disease progression, and therapy should be titrated to achieve as normal an albumin-to-creatinine ratio as possible."[7]

Additional relevant issues noted in the ADA statement "Care of Children and Adolescents with Type 1 Diabetes" include[7]:

- Concomitant hypertension should be addressed. If present, hypertension should be aggressively treated to achieve normotension for age, sex, and height.
- Patients should be educated about the importance of attention to glycemic control and avoidance or cessation of smoking in preventing and/or reversing diabetic nephropathy.
- If medical treatment is unsatisfactory, referral to a nephrologist should be considered.

Depression

Depression is a significant comorbidity that can complicate the medical management of diabetes and is associated with poor adherence. Longitudinal studies of the association between T2DM and depression among youth are not available. In a longitudinal study among youth with T1DM, however, Kovacs et al[67] estimated the rate of psychiatric disorders to be 3 times higher in youth with diabetes than in those without diabetes, with the increased morbidity primarily attributable to major depression.[7,67,68] In addition, cross-sectional data from the SEARCH study have shown the prevalence of depressed mood to be higher among males with T2DM than among males with T1DM.[67] Lawrence et al[68] also found higher levels of depressed mood to be associated with poor glycemic control and number of emergency department visits among participants with both T1DM and T2DM, compared with youth with T1DM and T2DM who had "minimal" levels of depressed mood.

Because depression is associated with poor adherence to diabetic treatment recommendations, its identification and proper management are essential for maximizing therapeutic success. Given the serious nature of this comorbidity and its propensity for poor metabolic control, the committee recommends that clinicians assess youth with T2DM for depression at diagnosis; perform periodic, routine screening for depression on all youth with T2DM, especially those with frequent emergency department visits or poor glycemic control; and promptly refer youth who have positive screenings to appropriate mental health care providers for treatment. Addressing a family history of diabetes and its effect on the family unit can be a major factor in depression as well as compliance with the disease management needs.

Screening:

- According to the American Psychiatric Association, a diagnosis of major depressive disorder requires[69]:
  (a). The presence of 5 or more of the following symptoms within the same 2-week period and represents a change from previous functioning. At least 1 of the symptoms is either depressed mood or loss of interest or pleasure.
- Depressed mood most of the day, nearly every day, as indicated by either substantive report or observation made by others. (Note that in children and adolescents, this can be irritable mood.)
- Markedly diminished interest or pleasure in all, or nearly all, activities most of the day, nearly every day.
- Significant weight loss when not dieting or weight gain (eg, more than 5% of body weight in a month), or increased or decreased appetite nearly every day. (Note that in children and adolescents, this should include failure to make expected weight gains.)
- Insomnia or hypersomnia nearly every day.
- Psychomotor agitation or retardation nearly every day (observable by others, not merely the subject's feeling restless or slowed down).
- Fatigue or loss of energy nearly every day.
- Feelings of worthlessness or inappropriate guilt (which may be delusional) nearly every day.
- Diminished ability to think or to concentrate, or indecisiveness, nearly every day.
- Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt, or a specific plan to commit suicide.

(b). The symptoms do not meet the criteria for a mixed episode (defined as a specific time period in which the individual experiences nearly daily fluctuations in mood that qualify for diagnoses of manic episode and major depressive episode).

(c). The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

(d). The symptoms are not due to the direct physiologic effects of a substance (eg, a drug of abuse, medication) or a general medical condition (eg, hypothyroidism).

(e). The symptoms are not better accounted for by bereavement (ie, after the loss of a loved one), symptoms persist longer than 2 months, or symptoms are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

- Another potentially valuable screening tool for depression is the Center for Epidemiologic Studies Depression Scale (CES-D), a 20-item scale originally developed for use in adults[70] but which has been used subsequently in studies of youth as young as 12 years.[71–74] (See Supplemental Information G for this scale.)

Treatment:

- Recognition of depression should trigger a referral to a mental health care provider skilled in addressing this condition in children and adolescents.

Other Comorbidities or Associated Medical Conditions

In addition to the comorbidities mentioned previously, T2DM is associated with other obesity-related medical conditions, many of which, when discovered, necessitate consultation with specialists who have specific expertise in the field. These associated conditions include:

- Nonalcoholic fatty liver disease: Baseline aspartate aminotransferase and alanine aminotransferase concentrations should be obtained, especially if treatment with lipid-lowering drugs is instituted. Referral to a pediatric or internal medicine gastroenterologist may be indicated.
- Obstructive sleep apnea: The diagnosis of obstructive sleep apnea can only be made reliably by using a sleep study. If the diagnosis is made, an electrocardiogram and possibly an echocardiogram should be obtained to rule out right ventricular hypertrophy. Referral to a pediatric cardiologist, internal medicine cardiologist, or sleep specialist may be indicated.
- Orthopedic problems: These comorbidities (especially slipped capital femoral epiphysis and Blount disease) require immediate referral to a specialist in orthopedics and will limit the physical activity that can be prescribed to the individual.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

The clinical practice guidelines do not present any evidence-based recommendations for the use of complementary and alternative medicine (CAM) to treat T2DM in children and adolescents. Limited data are available on CAM, and none is specific to this age group. However, noting that adult patients with diabetes are 1.6 times more likely to use CAM than are individuals without diabetes, the committee believes it is important for clinicians to encourage their patients to communicate openly about the use of CAM (especially because the parents may have diabetes themselves) and, when acknowledged, to differentiate between coadministration with the prescribed therapy versus replacement of (and, thus, noncompliance with) the prescribed therapy.[75]

CAM is most likely to be used by West Indian, African, Indian, Latin American, and Asian subjects.[76] CAM is also more common in families with higher income and education levels and an increased interest in self-care. One multicenter study conducted in Germany found that, among 228 families with a T1DM diagnosis, 18.4% reported using at least 1 form of CAM.[77] Reported parental motivators for using CAM for their children included the hope of improving their well-being (92.1%); the desire to try every available treatment option (77.8%); and the assumption that CAM has fewer adverse effects than conventional therapy (55.2%). Many forms of CAM are used because of patient-perceived inadequacies of current treatments.[75]

A wide variety of CAM dietary supplements are targeted at patients with diabetes and promise to lower BG concentrations or prevent and/or treat complications associated with the disease. Common supplements used by individuals with diabetes include aloe, bitter melon, chromium, cinnamon, fenugreek, ginseng, gymnema, and nopal.[78] These products lack product standardization and are not regulated by the US Food and Drug Administration for either safety or possible complications. Although these supplements may or may not have proven beneficial effects on diabetes, many might have harmful adverse effects and/or lead to medication interactions. Adverse effects from dietary supplements can include gastrointestinal discomfort, hypoglycemia, favism, insomnia, and increased blood pressure.[78]

In addition to dietary supplements, patients may use forms of CAM that include prayer, acupuncture, massage, hot tub therapy, biofeedback, and yoga. The University of Chicago's Division of Pediatric Endocrinology interviewed 106 families with T1DM and found that 33% of children had tried CAM in the past year; the most common form used was faith-healing or prayer.[79] Parents who reported the use of CAM for their children were also more likely to report having experienced struggles with adherence to conventional medicine.

It is the committee's opinion that providers should question patients on their use of CAM and also educate patients on potential adverse effects, review evidence for efficacy, and discourage the use of potentially dangerous or ineffective products.

SUMMARY

The clinical practice guideline that this technical report accompanies provides evidence-based recommendations on the management of patients between 10 and 18 years of age who have been diagnosed with T2DM. The document does not pertain to patients with impaired glucose tolerance, isolated insulin resistance, or prediabetes, nor does it pertain to obese but nondiabetic youth. It emphasizes the use of management modalities that have been shown to affect clinical outcomes in this pediatric population. The clinical practice guideline addresses situations in which either insulin or metformin is the preferred first-line treatment of children and adolescents with T2DM. It suggests integrating lifestyle modifications (ie, diet and exercise) in concert with medication rather than as an isolated initial treatment approach. Guidelines for frequency of monitoring HbA1c and finger-stick BG concentrations are presented. The clinical practice guideline is intended to assist clinician decision-making rather than replace clinical judgment and/or establish a protocol for the care of all children with this condition. These recommendations may not provide the only appropriate approach to the management of children with T2DM. Providers should consult experts trained in the care of children and adolescents with T2DM when treatment goals are not met or when therapy with insulin is initiated.

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SUBCOMMITTEE ON TYPE 2 DIABETES (OVERSIGHT BY THE STEERING COMMITTEE ON QUALITY IMPROVEMENT AND MANAGEMENT, 2008–2012)

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Janet Silverstein, MD, FAAP: Co-chair—Endocrinology and American Diabetes Association Liaison (small grants with Pfizer, Novo Nordisk, and Lilly; grant review committee for Genentech; was on an advisory committee for Sanofi Aventis, and Abbott Laboratories for a 1-time meeting); published research related to type 2 diabetes

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