

AMERICAN ACADEMY OF PEDIATRICS

CLINICAL REPORT

Guidance for the Clinician in Rendering Pediatric Care

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Prevention and Treatment of Type 2 Diabetes Mellitus in Children, With Special Emphasis on American Indian and Alaska Native Children

ABSTRACT. The emergence of type 2 diabetes mellitus in the American Indian/Alaska Native pediatric population presents a new challenge for pediatricians and other health care professionals. This chronic disease requires preventive efforts, early diagnosis, and collaborative care of the patient and family within the context of a medical home. *Pediatrics* 2003;112:e328–e347. URL: <http://www.pediatrics.org/cgi/content/full/112/4/e328>; type 2 diabetes mellitus, children, American Indian, Alaska Native, Native American, pediatric population.

ABBREVIATIONS. AI/AN, American Indian/Alaska Native; AAP, American Academy of Pediatrics; IHS, Indian Health Service; CDC, Centers for Disease Control and Prevention; ADA, American Diabetes Association; PCOS, polycystic ovarian syndrome; BMI, body mass index; HbA_{1c}, glycosylated hemoglobin; OGTT, oral glucose tolerance test; FBG, fasting blood glucose; FPG, fasting plasma glucose; SMBG, self-monitoring of blood glucose; ACE, angiotensin-converting enzyme; LDL, low-density lipoprotein; HDL, high-density lipoprotein; NDEP, National Diabetes Education Program; NPH, neutral protamine Hagedorn; TZD, thiazolidinedione.

STATEMENT OF THE PROBLEM

Type 2 diabetes mellitus* is a new morbidity in children and adolescents.^{1–4} For pediatric patients, it heralds earlier onset of cardiovascular disease, retinopathy, nephropathy, and neuropathy, with risk of impaired quality of life and premature death. The emergence of type 2 diabetes mellitus in young people is believed to be associated with changes in physical activity and nutrition that are ubiquitous in modern society. Not all populations are equally affected. American Indian/Alaska Native (AI/AN) children in the United States and Canada have a higher rate of this disease than do children of other ethnicities. Mexican American and

black children are at increased risk. Vulnerable populations that exhibit new disease trends may be seen as the “canary in the coal mine,” warning of hazards present for the entire population. In US children, the prevalence of type 2 diabetes mellitus is expected to exceed that of type 1 diabetes mellitus within 10 years. There is a compelling need for additional research, primary and secondary prevention efforts, and evidence-based treatment for youth with type 2 diabetes mellitus.

PURPOSE

These guidelines have been developed to assist in clinical decision making by primary health care professionals and are not intended to replace existing management protocols for the medical treatment of diabetes.⁵ It is assumed that clinical care will be individualized for each child and adolescent. In keeping with the spirit of community pediatrics and the *Healthy People 2010* objectives, the American Academy of Pediatrics (AAP) believes that medical care for AI/AN children, like that of all other children, should be provided within a medical home, which “ideally should be accessible, continuous, comprehensive, family centered, coordinated, compassionate, and culturally effective. It should be delivered or directed by well-trained physicians who provide primary care and manage and facilitate essentially all aspects of pediatric care. The physician should be known to the child and family and should be able to develop a partnership of mutual responsibility and trust with them.”⁶

METHODS

The AAP Committee on Native American Child Health, in collaboration with the Indian Health Service (IHS) Diabetes Program, the Centers for Disease Control and Prevention (CDC), and the AAP Section on Endocrinology, developed these guidelines to improve the medical care for AI/AN children with type 2 diabetes mellitus and those at risk of type 2 diabetes mellitus. This effort was greatly assisted by the 2000 American Diabetes Association (ADA) consensus statement on type 2 diabetes mellitus in children and adolescents.^{2,3}

These guidelines were developed after a review of published data on type 2 diabetes mellitus in American Indian and First

The recommendations in this report do not indicate an exclusive course of treatment or serve as a standard of care. Variations, taking into account individual circumstances, may be appropriate.

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*Type 1 diabetes mellitus is characterized by a lack of insulin production. Type 2 diabetes mellitus is a metabolic disorder secondary to an inability to appropriately use or make adequate insulin.

Nations† children⁷⁻²³ and are adapted from the medical literature on adults with type 2 diabetes mellitus.^{5,24-29}

These guidelines were developed to support the role of the general pediatrician or other primary health care professional as the front line for care. The treatment of most AI/AN children with type 2 diabetes mellitus will be managed by primary health care professionals with specialty consultation. It is hoped that these guidelines will serve as a framework for the development of diabetes care programs and strategies aimed at decreasing the devastating impact of type 2 diabetes mellitus on AI/AN children and their families and communities. A section on primary prevention of type 2 diabetes mellitus is included and is based on existing data.

PRIMARY AND SECONDARY PREVENTION

Prevention must take highest priority and should focus on decreasing the risk, incidence, and consequences of type 2 diabetes mellitus among AI/AN children. Primary prevention efforts by primary health care professionals are recommended in 2 arenas: 1) general community health promotion and health education and 2) clinically based activities. Clinically based health promotion activities should not duplicate community-wide health promotion but instead should offer additive benefits. For example, if significant health education is offered at the community level, then motivational interviewing and collaborative problem solving can be offered in the clinical setting. When type 2 diabetes mellitus is the established diagnosis, secondary prevention efforts by primary health care professionals are important for the prevention of complications (eg, vascular, neural, renal, retinal). Early diagnosis and optimal medical care are the keys to effective secondary prevention.

To be effective, prevention efforts need a strong community base and acceptance. Current evidence suggests that modifiable risks for type 2 diabetes mellitus include obesity and lack of breastfeeding.³⁰ Primary prevention efforts can focus on the prevention of obesity in children and the promotion of breastfeeding. Preventing obesity in women of child-bearing age is another primary prevention goal, because exposure to the environment of a diabetic pregnancy places the fetus at increased risk of future onset of diabetes.³⁰

Community Activities

Community prevention activities are being developed in AI/AN communities on the basis of each tribe's unique needs and resources. Development and implementation of these activities should have the endorsement of appropriate tribal authorities. Ideally, these activities are multidisciplinary (eg, medical, nutrition, public health, nursing, health education) and include local businesses, community recreational programs, Head Start programs, and schools.^{31,32} Tribal food and nutrition programs (eg, Special Supplemental Nutrition Program for Women, Infants, and Children; US Department of Agriculture's Food Distribution and Food Stamp program) have a prominent role in promoting foods that minimize the risk of obesity. Community pro-

grams and services should develop consistent messages and supply foods that assist in decreasing the prevalence of obesity. Studies to evaluate the effectiveness of community-based obesity and diabetes risk reduction efforts are in progress.^{33,34}

Health care professionals can play a crucial role in their communities by raising community awareness about the importance of programs and facilities for physical activity and resources for healthy nutrition.³⁵ The powerful influence of physicians extends outside the clinic when they thoughtfully advocate for healthy lifestyles and good nutrition practices within the community.

Pediatricians and other health care professionals should advocate for school policy that requires daily physical activity for every child and for physical fitness programs in the school and community. They should urge stores, restaurants, and schools to offer low-caloric density foods of high nutritional value in appropriate portions. Lack of physical activity is associated with the development of obesity, type 2 diabetes mellitus, and cardiovascular morbidity and mortality. Despite information on the importance of exercise, a low proportion of high school students participate in daily physical education classes.^{36,37} Increasing physical activity should include participating in at least 30 minutes of physical activity daily, limiting sedentary activity (eg, watching television, playing video games, using a computer) to no more than 1 to 2 hours per day, and participating in sports. Community recreation programs and schools should encourage youth to participate in events that require physical activity. The community leadership should receive information on and understand the importance of physical activity and the value of having programs and facilities available for youth. Recommendations and programs should respect family, culture, and community values.

Health care professionals can use their expertise to provide prevention messages to the community on healthful lifestyles and good nutrition via local media (eg, radio, television, newspapers, posters). Prevention messages need to be thoughtfully developed to resonate with community and tribal culture and beliefs. Youth involvement in community prevention efforts can be highly effective.

Community involvement in the promotion and support of healthful lifestyles reinforces recommendations made in the health care setting. The engagement and empowerment of communities is critical for overall success in decreasing the disease burden of type 2 diabetes mellitus for the AI/AN population. Schools are integral in the successful management of type 2 diabetes mellitus (and other chronic illnesses) and potentially are important resources for promoting children's diabetes self-care, including blood glucose monitoring, appropriate recognition and treatment of hypoglycemia, and treatment of acute hyperglycemia.

Clinically Based Primary and Secondary Prevention Activities

Health care professionals have influential roles in preventing type 2 diabetes mellitus among at-risk

†First Nations is the term used in Canada to identify Native or Aboriginal people. In this article, this term is used when citing research done in Canada.

youth via direct patient care contacts. Children with 1 or more risk factors (see "Case Finding") identified by the ADA consensus panel on type 2 diabetes mellitus in children should be monitored closely.^{2,3} Identification of disorders associated with insulin resistance, such as acanthosis nigricans, polycystic ovarian syndrome (PCOS), and family history of diabetes, should trigger education and the initiation of prevention activities.

Children whose body mass index‡ (BMI; see also "Physical Assessment") is greater than the 85th percentile for their age§ should receive appropriate counseling on nutrition, weight control, and physical activity. This is especially important because there is evidence that type 2 diabetes mellitus can be delayed or prevented by lifestyle interventions. These children may require treatment for hypertension and hyperlipidemia and should return for follow-up evaluation and additional lifestyle intervention within 3 months.

Until results of current prevention trials with oral hypoglycemic agents in youth are available, intervention using glucose-lowering drugs for prevention of diabetes is not recommended. (These medications are, however, recommended for treatment of children with diagnosed type 2 diabetes mellitus.)

Knowledgeable health care professionals (eg, nutritionists, health educators, physicians, nurses, community outreach workers) should guide nutrition interventions in AI/AN children and their families. Any intervention needs to consider growth and development in children. The most effective approach is appropriate reduction of calories along with increased energy expenditure. Specific recommendations need to be individualized, and continued evaluation is crucial for long-term success. Individualized plans are based on collaboration with the child and the family to assess food preferences, timing and location of meals and snacks, food preparation, and desire to change behaviors. Family resources and the availability of low-calorie nutritious foods in the community must be considered. Pharmacologic therapy to decrease weight is not recommended for children until more safety and efficacy data are available. Very low-calorie diets and high-protein diets are contraindicated, except in a well-controlled research setting. Quick-fix weight loss programs are unsafe for children and rarely result in long-term weight control; furthermore, they do not promote lasting, healthful eating behaviors. Weight loss programs with the best results combine exercise and dietary components with behavior modification.³⁸ Accomplishing changes in the child's eating behavior and activity relies on changes made by the entire family.

‡BMI is a measure based on weight and stature (kg/m²). A simple calculation can be made as follows: weight in pounds divided by height in inches, divided by height in inches again, and multiplied by 703.

§Growth charts developed by the CDC; see "Physical Assessment" for Web site address.

IDENTIFICATION

The prevalence of type 2 diabetes mellitus in AI/AN children as well as AI/AN adults is higher than among other ethnic groups.^{2,3,18} Among Pima Indian adolescents 15 to 19 years of age, the prevalence of type 2 diabetes mellitus estimated through screening increased significantly during the past 2 decades and reached 5% in the 1992–1996 time period.¹⁹ (Although population-based prevalence estimates are not available for children and adolescents in the United States, a retrospective review estimated an incidence of 7.2 per 100 000 for black and white children and adolescents in southwestern Ohio in 1994.²⁰) In Manitoba, Canada, the prevalence of type 2 diabetes mellitus diagnosed through screening was 3.6% for First Nations girls (0% for boys) 10 to 19 years of age in 1996–1997.¹⁵ The prevalence of diagnosed diabetes (all types) among youth 15 to 19 years of age receiving services from the IHS was 0.45% in 1996, reflecting a 54% increase since 1988.²¹ In Montana and Wyoming IHS clinics, the prevalence of diagnosed diabetes (all types) was 0.23% among American Indian youth 0 to 19 years of age in the period 1997–1999.^{22,23} Therefore, the high burden of diabetes on AI/AN communities and their youth deserves specific research efforts directed toward better case identification.

Population-Based Screening

Many AI/AN communities are interested in population-based screening for type 2 diabetes mellitus. The evidence that microvascular complications of diabetes are strongly associated with previous hyperglycemia raises interest in earlier diagnosis during the asymptomatic period.³⁹ However, population-based screening for type 2 diabetes mellitus in high-risk children is not recommended, except as part of research efforts to advance knowledge about optimal prevention, diagnosis, and treatment.^{40–43} Population-based screening remains controversial, because there are no data from controlled trials showing that earlier diagnosis improves long-term outcome. It is essential that studies be performed to determine the specificity, sensitivity, and cost-benefit of screening for type 2 diabetes mellitus in high-risk populations of children and adolescents.

The World Health Organization has recommended that before embarking on population-based screening, the following criteria be met⁴⁴:

1. The condition should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be understood adequately.

8. There should be an agreed policy on whom to treat as patients.
9. The cost of case finding should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case finding should be a continuing process and not a once-and-for-all project.

Although some of these criteria can be met, a key aspect to the second criterion is that there must be evidence that earlier identification improves clinical outcomes before the costs of this endeavor can be justified under nonresearch protocol.⁴⁴ The first results from the Diabetes Prevention Program show that diet and exercise delay the onset of diabetes and normalize blood glucose in adults.⁴⁵ Therefore, it is important to identify children and adolescents who are at risk of developing diabetes, such as those with obesity and signs of insulin resistance, to begin lifestyle management programs that could prevent and delay the development of diabetes. Many of these children will have impaired glucose tolerance.

Before beginning screening programs, health care systems and institutions must identify resources for intervention for people who will be identified with type 2 diabetes mellitus or altered glucose metabolism by the screening program. Screening programs can cause harm if effective treatment is not available.

If universal screening were performed in the United States on the basis of the ADA risk criteria for type 2 diabetes mellitus in youth, then 10% of US adolescents (2.5 million) 12 to 19 years of age would be tested.⁴³ This screening would not yield a large number of new diagnoses because of the low prevalence of type 2 diabetes mellitus in the general adolescent population.⁴⁶

Screening efforts have been implemented as part of research initiatives for some high-risk populations. Among the Pima Indians, screening has been performed by the National Institutes of Health since 1965 as part of a longitudinal epidemiologic study. Because of the high prevalence of type 2 diabetes mellitus among Pima Indian children identified by the epidemiologic study, current efforts focus on measuring glycosylated hemoglobin (HbA_{1c}) concentration in children who are at risk and referring them for a 2-hour oral glucose tolerance test (OGTT) if the HbA_{1c} concentration is more than 5.5%.¹⁸ Another survey conducted in 1996–1997 in 717 First Nations school youth 4 to 19 years of age from Manitoba identified 6 new cases and 2 previously identified cases by using the fasting blood glucose (FBG) concentration.¹⁵ A survey of 276 Navajo students 13 to 20 years of age at 2 high schools found 1 case of diabetes and 8 cases of impaired glucose tolerance or impaired FBG concentration.⁸ Future studies may identify specific criteria for screening children for type 2 diabetes mellitus in AI/AN populations.

Earlier diagnosis of diabetes may prevent or slow the development of complications if active treatment is implemented early and proves efficacious. In a world of limited resources, the benefits of screening efforts need to be assessed and balanced with those

of other programs that may benefit the same population.

Some IHS areas and Indian tribes are developing screening and intervention programs for obesity and hypertension in youth. These efforts will result in identifying youth who are at increased risk of type 2 diabetes mellitus and have the potential to benefit from primary prevention interventions.

Case Finding

Although population-based screening is not recommended, early case finding and early initiation of treatment may prevent some sequelae of type 2 diabetes mellitus. Overweight children who have entered puberty (or who are older than 10 years) are considered at risk by the ADA if they meet 2 of the following criteria^{2,3}:

- Family history of type 2 diabetes mellitus in first- or second-degree relative
- Race or ethnicity is American Indian, Alaska Native, black, Hispanic, or Asian/Pacific Islander
- Presence of a condition associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, PCOS)

The following are definitions for being at risk for overweight⁴⁷:

- BMI between the 85th and 95th percentiles for age and sex
- Weight-for-height ratio between the 85th and 95th percentiles

The following are definitions for being overweight:

- BMI greater than the 95th percentile for age and sex
- Weight-for-height ratio greater than the 95th percentile
- Weight greater than 20% of the ideal weight for height

The term “obese” is not defined for children by the CDC. Health care professionals should be knowledgeable about risk factors and make appropriate decisions to test individual patients.

Diagnosis (Clinic Based)

The diagnosis of type 2 diabetes mellitus in a child or an adolescent usually will be made by an astute health care professional in a clinical setting rather than as a result of a screening program. Knowledge of the aforementioned risk factors will assist the health care professional in considering and making the diagnosis when the patient is asymptomatic. Symptomatic and asymptomatic disease manifestations are described in “Pharmacologic Management on the Basis of Clinical Manifestations.”

Specialists should be consulted for children and adolescents in whom diabetic ketoacidosis is detected. Furthermore, subspecialty consultation is indicated for children with hyperglycemia (FBG >250 mg/dL [>13.9 mmol/L]) but without the clinical features, family history, or physical characteristics

commonly associated with type 2 diabetes mellitus. In such cases, diagnostic differentiation between type 1 and type 2 diabetes mellitus may require additional studies, such as autoimmune markers (islet cell antibodies, glutamic acid decarboxylase antibodies), challenge tests with high-calorie nutritional supplements (eg, Sustacal and Boost Nutritional Energy Drink [Mead Johnson Nutritionals, Evansville, IN]) or glucagon, or assays of insulin or C peptide. Children with type 2 diabetes mellitus may have normal or high C peptide and fasting insulin concentrations. However, children with type 2 diabetes mellitus with toxic effects of glucose attributable to prolonged hyperglycemia before diagnosis may have transient low insulin concentrations and may benefit from a short course of subcutaneous insulin therapy. Specialty consultation also should be sought when youth are unable to achieve treatment goals in a reasonable time frame or when complications occur. Specialty consultation is helpful for youth with hyperlipidemia and hypertension.

The subspecialist often is a pediatric endocrinologist. However, the primary health care professional (eg, pediatrician, family physician, internist) who is responsible for the diabetes clinic in an AI/AN health care facility may be a clinically competent expert in the management of type 2 diabetes mellitus. In geographically isolated locations, telemedicine may facilitate specialty consultation.

ONGOING EVALUATION AND MONITORING FOR TYPE 2 DIABETES MELLITUS IN CHILDREN

History and Psychosocial Assessment

A complete medical history, including a review of systems, is essential at diagnosis and at regular intervals (Table 1), with special attention to emotional disorders; eating disorders; alcohol, tobacco, and drug use; and family support. Emotional and behavioral disorders, particularly depression, have been associated with diabetes.^{48–57} Psychosocial assessment is recommended at diagnosis and informally at every visit. Assessment may be performed on the basis of patient history or by using a standardized screening tool.^{58,59} A social worker or a psychologist on the diabetes team can assist with this evaluation. If depression or another emotional disorder is identified, then treatment and referral should be initiated promptly.

Health care professionals and dietitians should screen for eating disorders as part of the standard nutrition evaluation for all children with type 2 diabetes mellitus.⁶⁰ Binge eating and bulimia are signif-

icant concerns. Psychiatrically defined eating disorders are differentiated from culturally normal behaviors, some of which may be unhealthful.

The use of alcohol, tobacco, and drugs should be evaluated in all children and adolescents in whom diabetes is newly diagnosed, and it should be reevaluated, at least informally, at every visit. The family's attitudes toward the use of these and other substances should be evaluated as well. Alcohol use may aggravate hypoglycemia caused by sulfonylureas or insulin and increase the risk of lactic acidosis in patients who use metformin.

Family support is essential to the child or adolescent with type 2 diabetes mellitus. The family's strengths and needs should be assessed so that necessary assistance can be offered. This assessment should include positive and negative role models in the home, availability of healthful foods (eg, fresh fruits and vegetables), financial resources, parental literacy, cultural beliefs about health and illness, and the family's understanding of diabetes. The involvement of the whole family in dietary and activity changes will promote successful management of the child's diabetes. A family history of diabetes and cardiovascular disease will influence the meaning of this illness within the family. Support services for the family may include health education, financial services, social services, mental health counseling, transportation, and home visiting. Socially disorganized families need early psychologic and social work intervention.

Physical Assessment

Although a complete physical examination is recommended for all children at diagnosis, special attention should be given to the following elements (Table 2).

Weight and height should be plotted on a growth chart. The weight goal should be based on BMI (weight [kg]/height² [m²]). (The Web site for growth charts⁶¹ is: www.cdc.gov/nchs/about/major/nhanes/growthcharts/charts.htm.) Weight should be measured at each visit, but height may be measured twice a year.

The blood pressure goal is less than the 90th percentile on the basis of height and weight standards. Blood pressure is assessed at each visit. Blood pressure control is discussed in "Reducing Cardiovascular Risk"^{62,63} (Table 3).

The skin, especially the back of the neck, the underarms, and the groin, should be evaluated for acanthosis nigricans, a thickened, hyperpigmented

TABLE 1. Ongoing Evaluation and Monitoring After Diagnosis: History

History Component	Frequency*	Recommendations
Interval history	Initially every 3 months ↓	Include ROS
Psychosocial assessment		May use standardized questionnaire ^{78,79}
Eating disorder		Binge eating, bulimia
Substance abuse		Alcohol, tobacco, drugs
Family assessment		Strengths, needs

ROS indicates review of systems.

* Frequency of detailed history may decrease in case of metabolic control and low-risk social circumstances to every 6 to 12 months.

TABLE 2. Ongoing Evaluation and Monitoring After Diagnosis: Physical Examination

Physical Examination Component	Frequency	Recommendations
Weight	Initially every 3 mo*	
Height, BMI	Initially every 3 mo*	
Blood pressure	Initially every 3 mo*	
Skin	Every 12 mo	Acanthosis nigricans, hirsutism, tinea, acne
Foot	Every 12 mo but visual foot check every 3 mo	Pedal pulses, neurologic examination, nails

* May decrease to every 6 months if linear growth is complete and glucose is well controlled.

skin condition (Fig 1). Acanthosis nigricans often correlates with high BMI and insulin resistance. The resolution of acanthosis nigricans may be a useful marker for decreasing insulin resistance.⁶⁴ Insulin resistance may improve as weight decreases. The improvement of the skin condition as a result of better metabolic control is highly desirable to adolescents. Therefore, identification of this condition is especially useful as a motivator for adolescents. Other treatable skin conditions may occur in association with insulin resistance, including tinea capitis, tinea corporis, and tinea pedis. Hirsutism or significant acne may be markers of hyperandrogenism in girls. Hirsutism is related to hyperinsulinism and is another potential motivating factor for adolescents to accomplish nutritional and physical activity goals.^{65–67}

A thorough visual inspection of the feet, including pedal pulses (posterior tibial and dorsalis pedis) and a neurologic examination are recommended shortly after diagnosis and then annually (Fig 2). The monofilament examination for foot sensation is included to assess protective sensation.⁶⁸ This examination is performed using the 5.07 (10-g) Semmes-Weinstein nylon monofilament mounted on a holder that has been standardized to deliver a 10-g force when applied properly. Because the sensory deficits appear first in the most distal portions of the foot and progress proximally in a “stocking” distribution, the toes are the first areas to lose protective sensation. The examination should include assessment for treatable nail conditions, such as paronychia and ingrown toenails. The main purpose of the foot examination in children is to teach that foot care is an important health habit.

A funduscopic examination with dilation to detect signs of diabetic retinopathy is recommended shortly after diagnosis and then annually by an experienced eye care professional.^{69,70}

Yeast vaginitis and balanitis are commonly seen in children and adolescents with type 2 diabetes mellitus.⁷¹ Inspection of the vulva and penis should be included in the physical examination to screen for these disorders. Tanner staging of children and adolescents with type 2 diabetes mellitus should be performed every 3 to 6 months until puberty is complete, because early onset of puberty is noted in overnourished children.^{72,73} A gynecologic examina-

tion for girls and a genital examination for boys may provide an opportunity to obtain additional sexual history and to offer abstinence and contraceptive counseling. Menstrual irregularities may be symptoms of PCOS in postpubertal girls.

Laboratory Evaluation

The fasting plasma glucose (FPG) concentration is the standard test for diagnosis. Monitoring is based on the FPG concentration and additional blood glucose measurements throughout the day. Fasting is defined as no consumption of food or any beverage other than water for at least 8 hours before testing. Most monitoring is performed by self-monitoring of blood glucose (SMBG) concentrations. Tables 4 and 5 include diagnostic and self-monitoring values.

The 2-hour postprandial glucose test provides information about glucose metabolism that is not provided by FPG measurement. It can be used for diagnosis together with FPG testing and must be used for monitoring.

Measurement of HbA_{1c} concentration should be performed quarterly. The results should be available at the time of the patient visit and discussed with the patient. Technology is available to perform rapid HbA_{1c} testing. Many diabetes clinics have standing orders for the performance of HbA_{1c} testing before the health care professional's consultation and discussion with the patient. The HbA_{1c} result can verify SMBG data and is useful for identifying the need to adjust insulin dosage when SMBG data are unavailable. Setting realistic short- and long-term goals in consultation with a pediatric endocrinologist or other health care professional knowledgeable about childhood type 2 diabetes mellitus is recommended whenever possible. The HbA_{1c} concentration goal is less than 7.0% (or <1% above the laboratory reference range). This may not be achievable for all patients. Realistic goals should be individualized for each patient. HbA_{1c} concentration greater than 8.0% is associated with a substantial increase in complications.⁷⁴ Any sustained decrease is beneficial.

It is important to screen for proteinuria at diagnosis and annually. Testing for microalbuminuria is indicated if proteinuria is absent. Microalbuminuria is a high urinary albumin concentration that is not detected on routine dipstick testing. Microalbuminuria is defined as a urinary albumin excretion of 20 to 200 μg per minute (30–300 mg per day). Annual screening for microalbuminuria permits early identification and treatment of patients who are at risk of nephropathy. The recommended method of detection is the measurement of the albumin-creatinine ratio in a spot urine collection. An alternative method uses reagent tablets or dipsticks that detect microalbuminuria. When positive, the results of rapid tests should be confirmed by the urinary albumin-creatinine ratio in a timed urine collection. A patient is not designated as having microalbuminuria unless 2 of 3 collections performed within a 3- to 6-month period show increased concentrations. This test is not valid if the patient has a urinary tract infection or during menses. Although microalbuminuria may be encountered in patients in whom type 2

TABLE 3. Classification of Hypertension

Age (Years)	High Normal (mm Hg)*	Significant Hypertension (mm Hg)†	Severe Hypertension (mm Hg)‡
6–9	Systolic: 111–121 Diastolic: 70–77	Systolic: 122–129 Diastolic: 70–85	Systolic: >129 (129)§ Diastolic: >85 (84)
10–12	Systolic: 117–122 Diastolic: 75–81	Systolic: 126–133 Diastolic: 82–89	Systolic: >133 (134) Diastolic: >89 (89)
13–15	Systolic: 124–135 Diastolic: 77–85	Systolic: 136–143 Diastolic: 86–91	Systolic: >143 (149) Diastolic: >91 (94)
16–18	Systolic: 127–141 Diastolic: 80–91	Systolic: 142–149 Diastolic: 92–97	Systolic: >149 (159) Diastolic: >97 (99)
>18	Not given Not given	Systolic: [140–179] Diastolic: [90–109]	Systolic: >(179) Diastolic: >(109)

* 90th to 94th percentile for age, boys and girls combined.

† 95th to 98th percentile for age, boys and girls combined.

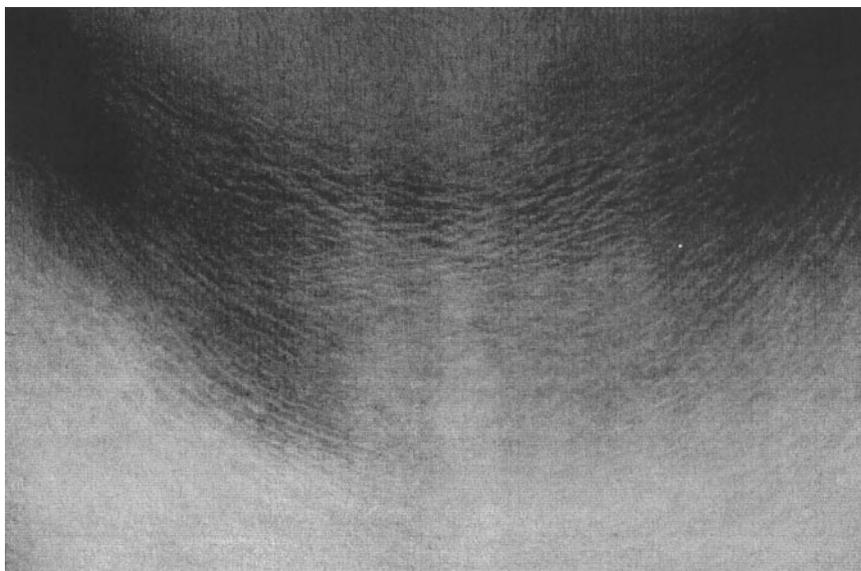
‡ 99th percentile for age, boys and girls combined.

§ The values in parentheses are those used for the classification of severe hypertension by the 26th Bethesda Conference on cardiovascular disease and athletic participation.

|| Because the Second Task Force did not discuss youth older than 18 years, the values in brackets are those for mild and moderate hypertension given by the 26th Bethesda Conference.

Adapted from American Academy of Pediatrics, Committee on Sports Medicine and Fitness. Athletic participation by children and adolescents who have systemic hypertension. *Pediatrics*. 1997;99:637–638

Fig 1. Acanthosis nigricans on the neck.



diabetes mellitus is newly diagnosed, proteinuria is the hallmark of diabetic nephropathy (Fig 3).^{19,75,76}

The serum creatinine concentration should be determined at diagnosis and when indicated for drug therapy. Annual serum creatinine screening is indicated for patients with hypertension or microalbuminuria and for people taking angiotensin-converting enzyme (ACE) inhibitors.

A fasting lipid profile, including total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglyceride concentrations, should be performed after diagnosis. The fasting lipid profile is best obtained after initial metabolic stabilization (1–3 months after diagnosis). The primary goal of therapy is to lower the LDL concentration,⁷⁷ which is discussed further in “Reducing Cardiovascular Risk.”

Liver function tests, including aspartate transaminase and alanine transaminase, should be performed before initiation of oral hypoglycemic therapy. Ad-

ditional monitoring may be required depending on the person’s drug regimen.

The concentrations of C peptide and insulin should not be measured routinely.^{2,3} When differentiation between type 1 and type 2 diabetes mellitus is difficult, consultation with a subspecialist with expertise in type 2 diabetes mellitus in children and adolescents is recommended. There currently is no definitive diagnostic tool to differentiate between type 1 and type 2 diabetes mellitus. The differentiation typically is made clinically on the basis of obesity, family history, ethnicity, age, pubertal status, and evidence of insulin resistance (eg, acanthosis nigricans, PCOS).

TREATMENT

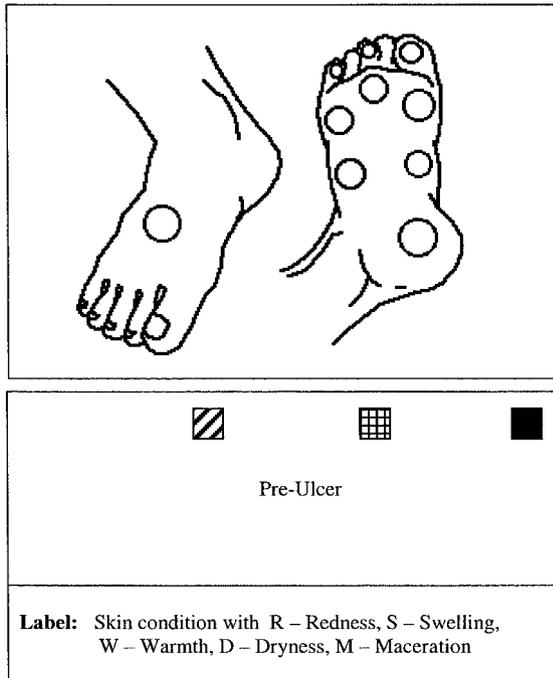
Goals of Treatment

The goals of treatment are adequate metabolic control (HbA_{1c} concentration <7%) and prevention of

Nail care _____

Shoes: adequate length and width _____

Diagram



	R	L
DP* pulse	_____	_____
Sensory Examination (5.07 monofilament, 10 g pressure)	_____	_____
Skin	_____	_____

*DP indicates dorsalis pedis.

Fig 2. Foot screening for youth with diabetes.

microvascular and macrovascular complications. More specific treatment objectives include the following:

- Eliminating symptoms of hyperglycemia
- Assisting the patient in maintaining a reasonable body weight (weight stabilization)
- Decreasing cardiovascular risk factors: hypertension, hyperlipidemia, hyperglycemia, microalbuminuria, sedentary lifestyle, and use of tobacco products
- Achieving overall improvement in the child's physical and emotional well-being

Recommended treatment modalities include dietary modification, increased physical activity, decreased sedentary behaviors, and pharmacologic intervention (primarily metformin and insulin). Therapy to achieve these goals should be individualized on the basis of the child's age, other illnesses, lifestyle, self-management skills, and level of motivation. Education and other interventions that en-

TABLE 4. Impaired Glucose Metabolism

Test	Impaired	Diagnostic for Diabetes
Fasting glucose	≥110 mg/dL and <126 mg/dL	≥126 mg/dL
Impaired 2-h OGTT	≥140 mg/dL and <200 mg/dL	≥200 mg/dL

hance self-care behaviors are essential for the successful management of type 2 diabetes mellitus. In general, weight loss is not recommended for prepubertal children. Children with morbid obesity and resultant health consequences, such as sleep apnea, may be referred to a subspecialist for weight reduction or a multidisciplinary child obesity clinic. Weight stabilization is the goal until girls are menstruating and boys have reached Tanner stage 5. After pubertal growth is complete, weight loss may be appropriate.

Barriers to Care

A functional and supportive environment is key in the treatment of children and adolescents with type 2 diabetes mellitus. One of the most serious barriers to achieving the goals of management is a dysfunctional family situation. The medical model of focusing only on the identified patient instead of treating the entire family further decreases the effectiveness of care.

Additional barriers exist for AI/AN youth. Environmental obstacles (eg, harsh climate, lack of transportation, limited access to healthy foods) create difficulties. Specific tribal or cultural issues, including beliefs and feelings about diabetes, may interfere with optimal self-care. For example, many families have a fatalistic attitude about diabetes: "My parents died of diabetes. I have it, and my children are going to get it." Eating and mood disorders, life stresses, and low self-esteem are common obstacles. Lack of appropriate role models, particularly healthy individuals living with diabetes, creates significant hardship for AI/AN children with diabetes. A low level of reading comprehension and proficiency in English may add additional barriers for some families. Furthermore, substance abuse is particularly problematic for many AI/AN children and their families. The health care system's frequent lack of understanding and respect for cultural beliefs may be a barrier to achieving optimal self-care. Many strategies have been shown to help overcome such barriers, including the use of trained professional interpreters, cultural competence and humility training for health care professionals and staff, and inclusion of members of the community in the design of clinical services.

Team Management

Multidisciplinary team management is strongly recommended for youth with type 2 diabetes mellitus. A primary health care professional alone usually cannot provide focused diabetes education, nutrition management, and psychosocial support. The team usually is composed of a physician, a registered di-

TABLE 5. Ongoing Evaluation and Monitoring After Diagnosis: Laboratory Evaluation*

Test	Frequency	Recommendations
SMBG	Fasting and 2-h postprandial glucose daily	Individualized
FPG test	Initially and ongoing	
2-h postprandial glucose test	At diagnosis and as needed	
HbA _{1c}	Every 3 mo	
Urinalysis	Every 12 mo	
Microalbuminuria	Every 12 mo	
Creatinine	At diagnosis	And per protocol if there is hypertension, microalbuminuria, or ACE inhibitor treatment
Lipid profile	At diagnosis and every 12 mo	
LFTs	At diagnosis	Before initiating oral hypoglycemic agents

LFT indicates liver function test.

*More frequent monitoring at diagnosis, during initiation of new treatment, and during metabolic changes (illness, stress, increased activity, and growth).

etitian, a nurse clinician, a social worker, and the patient and the family. The patient and the family are integral members of the team, and participation of the child or adolescent with the diabetes team should be frequent and ongoing. The diabetes team monitors the patient's knowledge about diabetes and its acute and chronic complications. The team also assesses and monitors the patient's knowledge and attitudes toward nutrition and physical activity. In addition, the team promotes the use of medications, SMBG, and problem-solving skills. Screening for barriers to self-care is recommended at each visit. The team assists in identification of achievable self-care goals that are appropriate for age and development level.

Many AI/AN health care facilities have existing diabetes clinics with multidisciplinary teams. It is highly recommended that these clinics organize a pediatric component so that youth receive developmentally appropriate care.

Lifestyle Modifications

The cornerstones of initial treatment of type 2 diabetes mellitus are acquiring and integrating healthful behaviors in nutrition, exercise, and weight management. Frequent contact with the health care team is required to accomplish these goals. The approach to healthful living must be emphasized throughout diabetes treatment. Initially, type 2 diabetes mellitus in asymptomatic youth may be managed by lifestyle modification without adjunctive medication. Basic diabetes education, counseling, and SMBG should be included. The natural history of type 2 diabetes mellitus is one of progressive insulin insufficiency and deterioration of metabolic control.^{78–84} Therefore, close monitoring and follow-up are important. Eventually, most people with type 2 diabetes mellitus require medication to achieve adequate metabolic control (Tables 4 and 5).

Resources

Many resources are available for health care professionals and their patients to help achieve therapeutic goals. However, there is a great need for more culturally sensitive educational materials. Information prepared for adults often is confusing to children and adolescents. Furthermore, resources for

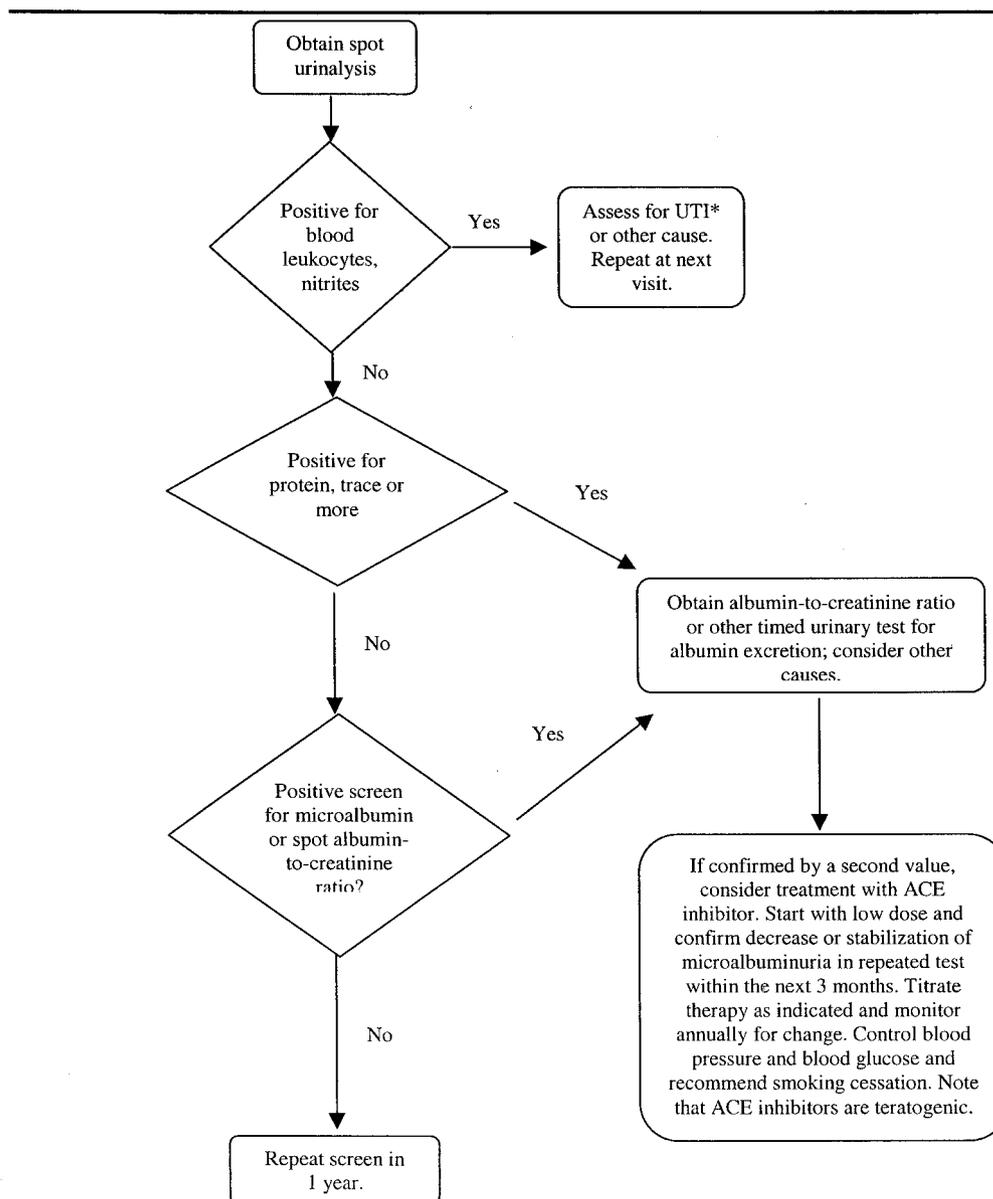
children and families with type 1 diabetes mellitus do not apply easily to families affected by type 2 diabetes mellitus.

The National Diabetes Education Program (NDEP) is a federally sponsored initiative of the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health, the CDC, and more than 200 public and private partners to improve treatment and outcomes for people with diabetes, promote early diagnosis, and, ultimately, prevent the onset of diabetes. The objectives of the NDEP are to:

- Increase public awareness of the seriousness of diabetes and its risk factors and strategies for preventing diabetes and its complications
- Improve understanding about diabetes and its control and promote better self-management behaviors among people with diabetes
- Improve health care professionals' understanding of diabetes and its control and promote an integrated approach to care
- Promote health care policies that improve the quality of and access to diabetes care

Target audiences include people with diabetes and their families (with special attention to Hispanic, black, and Asian Americans; Pacific Islanders; and the AI/AN population); the general public; health care professionals; and health care payers, purchasers, and policy makers.

The NDEP has convened a Diabetes in Children and Adolescents Work Group to address awareness and education issues related to children with diabetes, including the growing emergence of type 2 diabetes mellitus in youth. Furthermore, the NDEP American Indian/Alaska Native Work Group is focusing on youth with diabetes. The NDEP aims to assist health care professionals in increasing their knowledge about type 2 diabetes mellitus in children and adolescents; diabetes education materials for patients and health care professionals can be obtained from NDEP. For more information about the NDEP, see its Internet site at <http://www.ndep.nih.gov> or call 800-438-5383. Materials for educators about the management of diabetes in school settings are available.



* UTI indicates urinary tract infection.

Fig 3. Annual evaluation and treatment for microalbuminuria.

The ADA has a useful diabetes education program called WIZDOM, which includes specific patient education material in English and Spanish for youth with type 2 diabetes mellitus. Information can be found at the following Internet site: <http://www.diabetes.org/wizdom/pod.asp>.

MANAGEMENT TOOLS

Self-monitoring of Blood Glucose

The frequency of SMBG should be individualized. Daily fasting and 2-hour postprandial (after-dinner) glucose measurements are recommended.⁵ More frequent monitoring is recommended during initiation of treatment. Furthermore, monitoring frequency should be increased during the following situations: insulin treatment, medication dosage adjustments, initiation of new therapies, increased activity, rapid growth, illness, and emotional stress. The frequency

of SMBG may be negotiated with the patient and the family. For people who take insulin, the recommended frequency is before every meal and at bedtime. The recommended method is a blood glucose meter with memory. It can be instructive for patients to record their blood glucose results in a log to determine patterns. Reviewing these results with the patient at each visit is recommended. Many patients on medication will learn to make their own dosage adjustments on the basis of blood glucose patterns.

- Ideal targets: more than 50% of SMBG concentrations within target range:
 - ◆ Fasting: 80 to 120 mg/dL (4.4–6.7 mmol/L)
 - ◆ Postprandial (2 hours after start of meal): 100 to 160 mg/dL (5.6–8.9 mmol/L)
 - ◆ Bedtime: 100 to 160 mg/dL (5.6–8.9 mmol/L)

Medical Nutrition Therapy

Meal planning, nutrition education, and exercise are primary treatment strategies for type 2 diabetes mellitus. All people with diabetes should receive regular nutrition counseling and consult with a registered dietitian or nutritionist or a diabetes educator at least every 6 to 12 months. Some children may require more frequent evaluation and counseling. The success of the child in adopting healthful eating habits is much more likely when the entire family follows the dietary recommendations. Other family members may be able to serve as role models. Assisting the family and the patient in change related to eating behavior is recommended.⁸⁵ For example, some families will choose to purchase more fruits and vegetables and make them more readily available to all family members. Families may choose to discourage eating outside of mealtimes and make rules about limiting eating while watching television. Weight management must be individualized for the patient initially and in follow-up visits. Each encounter is an opportunity for nutritional education.

Diabetes Education

Patients and their families require diabetes self-care information that is culturally relevant. It is important to recognize that there are many different tribal cultures. The National Standards for Diabetes Care and Patient Education provide guidelines for education program development with criteria specific for Native American health care facilities.⁸⁶ In addition, adolescents have distinct needs related to the culture of youth.

Education alone is not enough to motivate people to adopt more healthful behaviors. Children and adolescents, in particular, are not easily motivated by long-term health consequences, which seem irrelevant to them. They are more likely to be influenced by immediate concerns, such as physical attractiveness, feelings of well-being and acceptance, and their desire to be able to do more in school or sports. The use of motivational interviewing or collaborative problem solving may be useful in helping children and adolescents make and maintain necessary behavior changes.

Physical Activity Education

Physical activity is a cornerstone of the management of type 2 diabetes mellitus. Physical goals should be stated concretely. Exercise is associated with improvement in short- and long-term metabolic control,^{87,88} and physical activity improves insulin sensitivity. All patients should be assessed for level of fitness and current exercise routines. Recommendations should be based on the patient's needs and current condition. It is important to assess the opportunities available within the family and the community. Adaptive physical education classes may be helpful for children who are overweight. Youth with obesity and type 2 diabetes mellitus are not likely to participate in organized sports, so other physical activity strategies are needed. Activities of daily living can be adapted to increase physical fitness.⁸⁸⁻⁹¹

Sedentary activities should be limited, and positive alternatives should be emphasized. When making behavioral changes, simple, achievable goals promote efficacy. Children and adolescents are more likely to accept fitness goals when they are framed in terms of feeling better, looking better, or doing more.³¹

Preconception Counseling and Management

A sexual activity history should be obtained at diagnosis in postpubertal youth. Counseling about the necessity of metabolic control for healthful pregnancy outcomes should start at puberty. Abstinence counseling should be provided, if appropriate. Family planning options should be discussed with adolescents who are or may become sexually active. Pregnancy should be deferred until optimal glycemic control has been achieved to decrease first-trimester risks to the fetus, including congenital heart disease, caudal regression, and neural tube defects, and third-trimester risks of macrosomia, neonatal hypoglycemia, and hypocalcemia, all of which are common in preexisting type 2 diabetes mellitus and gestational diabetes. All oral hypoglycemic agents are contraindicated during pregnancy. Furthermore, treatment of diabetes may increase fertility and the likelihood of pregnancy in young women. Metformin, in particular, may improve ovarian function and ovulation.

Immunizations

Usual childhood immunizations (including hepatitis B, influenza, and pneumococcal immunizations) are recommended. Tuberculosis screening by purified protein derivative should be documented once after the diagnosis of diabetes and performed at appropriate intervals, as indicated by community-specific tuberculosis prevalence.

Dental Examinations

Dental examinations are recommended every 6 months. Periodontal disease is more common in people with diabetes than in those without and has been called the sixth complication of diabetes (the other 5 complications involve the heart, kidney, eyes, skin, and feet).⁹²⁻⁹⁴

DECREASING CARDIOVASCULAR RISK

Identification and Treatment of Hyperlipidemia

Children with type 2 diabetes mellitus are at risk of hyperlipidemia, which compounds their risk of premature cardiovascular disease. Although the American Heart Association recommends that children's total cholesterol concentration be less than 170 mg/dL (<4.40 mmol/L) and the LDL concentration be less than 110 mg/dL (<2.84 mmol/L), the ADA recommends a lower target concentration for LDL in adults with diabetes^{28,87,95}: less than 100 mg/dL (<2.59 mmol/L). Because of the higher risk of cardiovascular disease in children with diabetes, the lower acceptable value recommended by the ADA is preferred. A lipoprotein analysis after a 12-hour fast is recommended to obtain triglyceride concentrations for computation of accurate LDL concentra-

tions,⁹⁵ although recent evidence indicates non-HDL cholesterol is a better predictor of atherogenesis than LDL cholesterol. If a fasting measurement is not possible, then a measurement of the HDL concentration, along with the total cholesterol concentration, will provide an alternative. Other reliable analyses of the lipid profile may become available in the future. Children with an LDL concentration more than 100 mg/dL (>2.59 mmol/L) or a total cholesterol concentration more than 170 mg/dL (>4.40 mmol/L) should receive advice about other risk factors for cardiovascular disease, such as smoking and sedentary lifestyle. High triglyceride concentrations are increasingly recognized as an additional cardiovascular risk factor for people with diabetes. In addition to studies showing the benefit of decreasing the cholesterol concentration in adults, the Bogalusa Heart Study provides evidence that risk factors, such as a low HDL concentration, high triglyceride and LDL concentrations, and smoking, have clinical significance for development of cardiovascular disease beginning in childhood.^{96–98}

The American Heart Association Step-One diet should be initiated for children with high total cholesterol or LDL concentrations. The Step-One diet includes fewer than 30% of total calories from fat, fewer than 10% of total calories from saturated fat, 10% or fewer calories from polyunsaturated fat, and cholesterol of no more than 100 mg/1000 cal. If cholesterol concentrations do not normalize despite a history of adherence to the Step-One diet, then the Step-Two diet is used. The Step-Two diet is lower in total cholesterol (67 mg/1000 cal) and saturated fat (<7% of total cal). People who follow these diets should be reevaluated every 6–12 months. More information about the Step-One and the Step-Two diets can be found on the American Heart Association's Internet site at <http://www.americanheart.org>. The assistance of a registered dietitian or other qualified nutrition professional is necessary to ensure adequacy of nutrients, vitamins, and minerals. Glycemic control, as well as therapy with metformin, can help to lower triglyceride and LDL concentrations. Cholesterol-lowering drug therapy should be considered for children older than 10 years if an adequate trial of diet therapy is unsuccessful after 6 to 12 months. An LDL concentration of 100 mg/dL or more (≥ 2.59 mmol/L) and 1 of the following risk factors or physical inactivity indicate a need for cholesterol lowering medication: family history of premature cardiovascular disease (55 years or younger), cigarette smoking, high blood pressure, low HDL concentration (< 35 mg/dL [< 0.91 mmol/L]), and obesity (≥ 95 th percentile weight for height).

The recommended cholesterol-lowering medications for children include cholestyramine and colestipol hydrochloride. These medications are difficult to take because of the frequency of dosing and adverse gastrointestinal effects. Although the efficacy and safety of these medications have been documented in children, long-term data on improved morbidity and mortality are lacking.⁷⁷ The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) are now approved for use in children who

have familial hyperlipidemia and are 10 years of age and older. They are being used and tested in pediatric populations for other indications. Rhabdomyolysis is a known adverse effect, and safety during pregnancy has not been proved. Specialty consultation may be helpful for treating youth with hyperlipidemia.

Blood Pressure Control

In adults, tight blood pressure control has been shown to have a greater impact on cardiovascular disease risk reduction than blood glucose control.^{99–102} Systemic hypertension is defined as systolic or diastolic pressure greater than or equal to the 95th percentile for age.¹⁰³ However, for children with type 2 diabetes mellitus, the blood pressure goal is less than the 90th percentile. Accurate blood pressure measurement is critical to the evaluation of suspected hypertension. The patient should be resting and comfortable. Cuff size, the position of the arm, the person's position (sitting or supine), and the speed of inflation and deflation of the cuff can affect the measurement. The cuff bladder width should be approximately 40% of the arm circumference midway between the olecranon and the acromion. The arm should be supported, and the cubital fossa should be at the level of the heart. The bell of the stethoscope should be placed over the brachial artery pulse. The cuff should be inflated to 20 mm Hg above the point at which the radial pulse disappears. The cuff is then deflated at a rate of 2 to 3 mm Hg per second. Automated devices are not as accurate for determining diastolic pressure. The diagnosis of hypertension should be confirmed in 3 separate consecutive examinations. For mild hypertension (slightly above the 95th percentile), the initial assessment should evaluate the possibility of renal disease. The evaluation of severe hypertension (≥ 99 th percentile for age) should include an echocardiogram.

Conservative management (eg, lifestyle changes, such as weight decrease in postpubertal patients, nutrition, and exercise) is recommended as initial therapy. Sodium restriction may be difficult for adolescents. Significant reduction in blood pressure may be noted with weight loss and exercise programs. If blood pressure reduction is not achieved by lifestyle changes, then drug therapy will be necessary. ACE inhibitors are the usual first-line agents because of cardiovascular and renal benefits.^{104,105} Because ACE inhibitors are teratogenic, another agent might be preferable for girls of childbearing age. Beta-blockers are an alternative unless the child is taking insulin, as symptoms of hypoglycemia may be masked.

Smoking and Alcohol Cessation and Prevention and Increasing Physical Activity

Smoking cessation and prevention of smoking initiation are essential for decreasing the risk of cardiovascular problems. Smoking is associated with an increased incidence of diabetes in adults.¹⁰⁶ It is important to screen for tobacco use and advise or refer for tobacco cessation if use is confirmed. Tobacco use information should be updated at each visit. Because

of the greatly increased risk of macrovascular and microvascular disease in people who have diabetes and smoke,¹⁰⁷ children and adolescents who do not smoke or use other tobacco products should receive positive reinforcement and information about the importance of continued abstinence.

Alcohol affects insulin production and increases insulin resistance, which also increases the risk of cardiovascular complications. The independent risk of cardiovascular complications associated with alcohol consumption by people with diabetes is a long-term hazard for youth with diabetes. A more immediate risk is hypoglycemia caused by alcohol consumption.

Alcohol use may aggravate the hypoglycemia caused by sulfonylureas or insulin treatment, and it may increase the risk of lactic acidosis for patients who use metformin. Alcohol and drug use should be assessed at every visit. Adolescents are at risk of substance abuse, which may interfere with the achievement of treatment goals. Anticipatory guidance regarding alcohol avoidance is recommended, including for children and adolescents who do not use alcohol or other drugs. The benefits of not drinking should be emphasized. The effectiveness of creative strategies should be evaluated.

Increasing physical activity is a positive way to decrease risk of cardiovascular complications.

Treatment of Microalbuminuria

Microalbuminuria is a sign of incipient diabetic nephropathy and is a risk factor for cardiovascular complications. Microalbuminuria may be encountered in people who have a new diagnosis of type 2 diabetes mellitus. Proteinuria, conversely, is the hallmark of diabetic nephropathy. ACE inhibitors are indicated for proteinuria or microalbuminuria and have been shown to slow the rate of progression of nephropathy in adults. Improved glycemic and blood pressure control slows the progression of nephropathy. ACE inhibitors are an additional important treatment modality, as shown in the evaluation and treatment algorithm (Fig 3).

PHARMACOLOGIC MANAGEMENT ON THE BASIS OF CLINICAL MANIFESTATIONS

The options for pharmacologic treatment include insulin; oral hypoglycemic agents, especially metformin; and any combination thereof. Intensive blood glucose control with insulin or sulfonylureas has been shown to decrease microvascular but not macrovascular complications.⁷⁹ The choice of medications is discussed in relation to the patient's status at diagnosis. The following sections are given in order of increasing severity and decreasing incidence.

Impaired Glucose Metabolism

Patients with impaired glucose tolerance and impaired fasting glucose have glucose concentrations too high to be considered normal but do not meet the diagnostic criteria for diabetes. They are considered to have prediabetes. Patients with impaired fasting

glucose have FPG|| concentrations of 110 mg/dL or more (≥ 6.1 mmol/L) but less than 126 mg/dL (< 7.0 mmol/L). Patients with prediabetes have 2-hour OGTT results between 140 and 200 mg/dL (7.8 and 11.1 mmol/L [Table 5]). Compared with the FPG, the 2-hour OGTT will identify more people as having impaired glucose tolerance. Although the 2-hour OGTT is more sensitive than the FPG, it is not as reproducible. It is, therefore, important to identify which test was used for diagnosis. An increase in the postprandial glucose concentration precedes an increase in the FPG concentration in adults. The natural history of impaired glucose tolerance in children and adolescents has not been studied. The US Diabetes Prevention Program has shown that lifestyle interventions are more effective than metformin and both approaches are more promising than conventional treatment in reducing progression to diabetes in adults with impaired glucose tolerance.¹⁰⁸ Similarly, a study of Finnish adults was interrupted because of the success of the lifestyle intervention arm.¹⁰⁹ Patients with prediabetes and their families should receive nutrition and physical activity intervention and support. Their risk of diabetes should be discussed. Monitoring of weight, nutrition, physical activity, and FPG should be performed regularly (at least every 3 months). Some diabetes centers recommend SMBG for high-risk patients with impaired glucose metabolism.

Asymptomatic Diabetes

People with diabetes may be identified as part of community-based case-finding efforts or by primary health care professionals who test asymptomatic children and youth who are at risk of type 2 diabetes mellitus. Patients with an FPG concentration of 126 mg/dL or more (≥ 7.0 mmol/L) or a 2-hour plasma glucose concentration of 200 mg/dL or more (≥ 11.1 mmol/L), using a glucose load of 75 g of anhydrous glucose dissolved in water, but who do not have polyuria, polydipsia, or weight loss are considered to have asymptomatic type 2 diabetes mellitus. When diabetes is identified early, treatment with lifestyle modifications and SMBG (fasting and postprandial) may be instituted. If plasma glucose or HbA_{1c} concentrations remain increased for 3 months, then treatment with oral agents or insulin should be started. Patients who attain euglycemia through lifestyle modification should be monitored every 3 months.

People with an FPG concentration greater than 250 mg/dL (> 13.9 mmol/L) should be treated as if they have symptoms, even if they report none.

Symptomatic Diabetes Without Ketoacidosis

Symptoms include polyuria and polydipsia, nocturia, sleep apnea, vaginitis, dysuria, and even weight loss. Many families do not recognize polyuria and polydipsia in adolescents. Educational ap-

||When glucose concentration is measured in a laboratory, plasma glucose concentration is measured. When a self-monitoring system is used, blood glucose concentration is measured; in most cases, these values are similar.

proaches to raise adolescent awareness about the potential significance of the symptoms of increased thirst and urination could encourage teenagers to alert their families and primary health care professionals.

Insulin

Initial treatment with subcutaneous insulin is suggested for children with FPG concentrations greater than 250 mg/dL (>13.9 mmol/L) and for children who are symptomatic. First Nations children with type 2 diabetes mellitus have been treated with subcutaneous insulin for 2 to 6 weeks followed by abrupt discontinuation of treatment with acceptable metabolic control.¹¹⁰

The use of insulin in children and adolescents with type 2 diabetes mellitus is safe.^{2,3,111–113} Preliminary data suggest that early insulin therapy may preserve beta cell function in type 1 diabetes mellitus. This may be true in type 2 diabetes mellitus as well.^{114,115} Symptomatic youth often have evidence of the toxic effects of glucose or a transient deterioration of beta cell function brought on by prolonged hyperglycemia. Thus, insulin often is needed for initial metabolic control. When C peptide or insulin concentrations are obtained at diagnosis, they may be uncharacteristically low. Therefore, if C peptide concentrations are measured to determine whether a patient has type 1 or type 2 diabetes mellitus, then it is best to wait until adequate metabolic control is obtained.

The recommended starting dose of insulin is individualized from 0.5 to 1.0 U/kg body weight per day. Additional insulin may be given if blood glucose concentrations do not fall below 150 mg/dL (8.3 mmol/L) before meals. Insulin dosage must be adjusted to achieve target blood glucose concentrations. Children and adolescents with type 2 diabetes mellitus often require much higher doses of insulin because of insulin resistance. Insulin regimens must be individualized. Some patients may require only intermediate-acting insulin (isophane [neutral protamine Hagedorn (NPH)] or lente) given once or twice daily. Others may require short- or rapid-acting insulin (regular or lispro/aspart) and intermediate-acting insulin (NPH or lente) with a distribution of two thirds of the total dose before breakfast and one third of the total dose before dinner.¹¹⁶ As with type 1 diabetes mellitus, an initial regimen might be to give the morning dose as one third regular or lispro/aspart and two thirds NPH or lente and the evening dose as one half regular or lispro/aspart and one half NPH or lente.¹¹⁷ It may be more physiologically appropriate to give the evening intermediate-acting insulin at bedtime.¹¹⁸ Lispro and aspart have certain advantages over regular insulin—its action profile provides insulin coverage for meals, and the dose can be adjusted according to the amount of food to be eaten. Other regimens that have proved successful are the use of the long-acting insulin glargine in conjunction with an oral hypoglycemic agent that increases endogenous insulin secretion to cover meals.

These dosage recommendations are to be considered a starting point, because insulin dosing must be adjusted on the basis of the blood glucose concentration. As metabolic control is achieved, insulin dosages start to decrease. It is not necessary to initiate insulin treatment with frequent dosing of rapid-acting insulin before meals. Using intermediate- and rapid-acting insulin early in treatment permits more rapid stabilization of glucose concentrations. When the health care professional judges that insulin will be required over the long-term, the person may be taught to give bolus insulin doses before meals, depending on the amount of carbohydrate to be consumed. Oral agents may be started once the glucose concentration is stabilized, and the insulin dosage gradually can be weaned. The glucose concentration usually is stable between 3 and 4 weeks after the initiation of therapy.²⁹

Oral Agents

The recently completed United Kingdom Prospective Diabetes Study demonstrated that type 2 diabetes mellitus is a progressive disorder that can be treated initially with oral agent monotherapy.^{79,80} Current recommendations for adults suggest beginning oral monotherapy if target glycemic goals are not achieved within 1 to 3 months of initial intervention of lifestyle modification. This period may not be practical for many AI/AN youth because of greater barriers to achieving activity and nutritional goals. A longer period may be warranted only if there is slow and steady improvement in achieving target glycemic goals.

Metformin is the only oral hypoglycemic agent approved for use in children. Data are not yet available regarding the safety, efficacy, or dosing of the other oral agents used to treat type 2 diabetes mellitus in children, although such data are available for adults. The biguanides (eg, metformin) and the sulfonylureas (eg, glyburide) have been part of the clinical experience in the treatment of type 2 diabetes mellitus in children. Sulfonylureas have been used for several years in the treatment of maturity-onset diabetes of youth, a set of rare, genetically determined diabetes. Use of metformin has increased in recent years, and clinical trials are in progress.

Metformin

The ADA consensus statement recommends that “if treatment goals with nutrition education and exercise are not met, pharmacologic therapy is indicated. The first oral agent should be metformin.”^{2,3,118} Metformin works by decreasing hepatic glucose production and enhancing insulin sensitivity. It is contraindicated for people with renal or hepatic disease, conditions that lead to hypoxia (eg, unstable asthma), or severe infection or those who abuse alcohol. It should be withheld before radiographic studies requiring the administration of radiocontrast dye. Metformin improves ovarian function, especially in women with PCOS, making family planning and contraception (when indicated) important. Lactic acidosis rarely has been reported.¹¹⁹ Gastrointestinal adverse effects, such as

abdominal discomfort and diarrhea, occur in approximately 20% to 30% of people who take metformin. These effects can be minimized by slowly titrating the dose and beginning with 250 mg each day, increasing to 250 mg twice daily, and finally increasing to 500 mg twice daily, if necessary. In adults, 80% to 85% of the maximal glucose-lowering effect is observed with a daily dose of 1500 mg. Most children who require treatment are at or above normal adult weight. Therefore, beginning at a dose of 500 mg per day would be considered safe. In adults, a clinically significant response at a dosage of less than 1500 mg per day is unusual. Metformin is supplied as 500- and 850-mg tablets and extended-release tablets. The maximum recommended daily dosage of metformin is 2550 mg. The current cost of metformin is approximately twice that of a second-generation sulfonylurea. However, less costly generic medications should soon be available. Advantages of metformin include decreased weight gain, possible weight loss, lower insulin concentrations, and improved lipid profile.^{29,120}

Sulfonylureas

The primary mechanism of action of the sulfonylureas is enhancement of insulin secretion. In adults in whom type 2 diabetes mellitus has recently been diagnosed, good results have been achieved with mild to moderate fasting hyperglycemia (220–240 mg/dL [12.2–13.3 mmol/L]), good beta cell function as reflected by a high fasting C peptide concentration, and the absence of islet-cell or glutamic acid decarboxylase antibodies. No sulfonylureas are currently approved for use in children, although studies in the pediatric population with second-generation agents are ongoing. In most studies in adults, sulfonylureas have had neutral or slightly beneficial effects on plasma lipid concentrations. Weight gain is common with use, a negative effect in patients in whom weight loss is a major goal. Most pediatric endocrinologists use sulfonylureas with other agents when monotherapy with metformin or insulin sensitizers has failed. First-generation sulfonylureas (chlorpropamide, tolazamide, acetohexamide, and tolbutamide) must be given in higher doses than second-generation sulfonylureas (glyburide, glipizide, and glimepiride). The second-generation sulfonylureas are largely free of drug interactions. The major adverse effect associated with sulfonylureas is

hypoglycemia. Most of the hypoglycemic action of the sulfonylurea is observed with a daily dose that represents half of the maximally effective dose. Sulfonylureas may potentiate the hypoglycemia associated with alcohol use. Therefore, alcohol consumption is contraindicated when a person is taking a sulfonylurea. Other adverse effects are uncommon but include nausea; vomiting; and skin reactions, including rashes, purpura, and pruritus. Leukopenia, thrombocytopenia, hemolytic anemia, and cholestasis have been reported. Although a 1970 study¹²¹ suggested that sulfonylureas may exacerbate coronary artery disease in people with type 2 diabetes mellitus, the ADA issued a statement in 1979 opposing any formal restrictions on use of the sulfonylurea agents on the basis of interpretation of that study. In addition, the United Kingdom Prospective Diabetes Study found no increased incidence of coronary artery disease for patients with type 2 diabetes mellitus who were assigned to intensive therapy with sulfonylureas, compared with patients who received dietary therapy without medications. The sulfonylureas have an additional advantage of low cost. Table 6 outlines the characteristics of select sulfonylureas.^{122,123}

Repaglinide

Repaglinide is a new agent. Like the sulfonylureas, it enhances the release of insulin, but the response is quicker and of shorter duration than that of sulfonylureas. Repaglinide's glucose-lowering effect is additive to the glucose-lowering effect of metformin. Furthermore, repaglinide has no significant effect on plasma lipid concentrations. Repaglinide must be taken before each meal because of its short duration of action. Thus, its primary effect is on the postprandial blood glucose concentration.

Thiazolidinediones

Thiazolidinediones (TZDs) work primarily by increasing insulin sensitivity in muscle and adipose tissue with a lesser effect on hepatic glucose uptake. The first TZD to be marketed in the United States, troglitazone, was taken off the market because of hepatotoxic effects. However, the newer agents in this class seem to have an improved safety profile. Although not approved for children, clinical trials in the pediatric population are in progress. Because TZDs increase insulin sensitivity, they have a favor-

TABLE 6. Pharmacologic Characteristics of Sulfonylureas¹²³

Characteristics	Tolbutamide	Tolazamide	Chlorpropamide	Glipizide	Glyburide
Relative potency	1	5	6	100	150
Duration of action (h)	6–10	16–24	24–72	16–24	18–24
Dose (mg)					
Range	500–3000	100–1000	100–500	2.5–40*	1.25–20
Average	1500	250	250	10	7.5†
Doses per day (n)	2–3	1–2	1	1–2	1–2
Dosage forms available (mg)	250, 500	100, 250, 500	100, 250	5, 10	1.25, 2.5, 5
Diuretic	Yes	Yes	No	No	Yes
Frequency of severe hypoglycemia (%)	1	1	4–6	2–4	4–6
Overall frequency of side effects (%)	3	4	9	6	7

* Studies have shown that the maximum effective dose of glipizide is 10 mg/dL. Doses above this may cause decreased efficacy.

† Glyburide is available worldwide as better-absorbed micronized preparations. These preparations are available in 1.5-, 1.75-, 3-, 3.7-, and 6-mg tablets.

able effect on HDL and triglyceride concentrations. Studies in adults indicate that TZDs result in a 1% to 2% decrease in HbA_{1c} values when used as monotherapy, although monotherapy is not recommended. Adverse effects include weight gain and fluid retention. TZDs may decrease the effectiveness of oral contraceptives. Another disadvantage is the high cost of this class of drugs. Dosing with pioglitazone hydrochloride is initiated at 15 mg daily with or without food. The dose can be increased after 8 to 12 weeks if the decrease in HbA_{1c} is inadequate. The maximum daily dosage is 45 mg for monotherapy and 30 mg for combined therapy. The dosage does not need to be adjusted for patients with renal disease. Pioglitazone is available as 15-, 30-, and 45-mg tablets. Rosiglitazone maleate initially is given as a single 4-mg dose. The dose may be increased to 4 mg twice daily or 8 mg daily if the response is inadequate after 8 to 12 weeks; however, the maximum dosage is 8 mg daily. Like pioglitazone, rosiglitazone can be given with or without meals and does not need dosage adjustment for patients with renal failure. It is available in 4- and 8-mg tablets.

Acarbose

The α -glucosidase inhibitor acarbose was introduced in the United States in the late 1990s. It primarily affects postprandial glucose concentrations by delaying carbohydrate digestion.^{124–126} Its major adverse effect, flatulence, has limited its acceptance in the pediatric population.

Combining Oral Agents

A maximal dose of a single oral agent (metformin or a sulfonylurea) may not maintain long-term acceptable glycemic control, according to ADA guidelines (FPG concentration <140 mg/dL [<7.8 mmol/L] or HbA_{1c} value <8.0%).¶ Because type 2 diabetes mellitus is a progressive disease with decreasing beta cell function, most people with an initial acceptable response to monotherapy will require additional agents as their disease progresses.^{127–129} Randomized, placebo-controlled studies of combination therapy support the effectiveness of this strategy for decreasing FPG and HbA_{1c} concentrations.^{130–132} When beta cells fail, insulin will need to be added to the therapeutic regimen.

Because metformin promotes weight loss and decreases lipid concentrations, it is preferred for use by overweight people with type 2 diabetes mellitus and dyslipidemia. The dose of metformin or sulfonylureas can be increased over a 4- to 8-week period until acceptable glucose control is achieved or the maximum dose is reached. If monotherapy fails with metformin, then a sulfonylurea should be added. It is prudent to assess whether the person is taking the medication as directed before initiating combination therapy. Patients may not take their medication for a variety of reasons, including denial of illness; fear of being labeled diabetic; fear of adverse effects, such as

hypoglycemia; actual adverse symptoms; and lack of knowledge about the need for long-term treatment. If combination therapy with 2 oral agents does not achieve the desired therapeutic goal, then bedtime insulin or a third oral agent may be considered. Referral to a specialist in type 2 diabetes mellitus for children and adolescents is recommended when combination therapy has failed.

Symptomatic Diabetes With Ketoacidosis

Diabetic ketoacidosis is defined by a bicarbonate concentration less than 15 mmol/L (<15 mEq/L) and/or pH less than 7.25. Type 2 diabetes mellitus may manifest with ketosis and, uncommonly, with ketoacidosis. Therefore, clinical presentation with ketoacidosis does not preclude the diagnosis of type 2 diabetes mellitus.

Insulin

Children with diabetic ketoacidosis require initial treatment with intravenous insulin followed by subcutaneous insulin. High doses may be required because of the insulin resistance characteristic of type 2 diabetes mellitus.¹³³ Health care professionals, nurses, and laboratory professionals who care for a large number of patients with diabetic ketoacidosis are more likely to have the necessary clinical competence to provide this high-acuity care. When care by such personnel is not possible, consultation with a subspecialist is recommended. Excellent treatment protocols and guidelines are available for the treatment of ketoacidosis.^{134–137} Once the patient's condition is stable, the important lifestyle modifications discussed previously can be addressed. As people often are willing to consider major lifestyle changes during a crisis, this may be an optimal teachable moment.¹³⁷

CONCLUSION

Type 2 diabetes mellitus in AI/AN youth is an alarming new morbidity that, without intervention, will lead to significant increased morbidity and mortality during adulthood. Health care professionals must address multiple medical and psychosocial concerns within the context of a medical home with the goal of coordinating comprehensive services from health care professionals and the community. Health care professionals who care for families affected by type 2 diabetes mellitus face the challenge of motivating people to adopt significant behavioral changes.

Several interventions have proved effective in preventing diabetes complications among adults, and evaluation of these interventions in children with type 2 diabetes mellitus is urgently needed. It is expected that clinical trials using behavioral and treatment interventions for children with diabetes will be developed. More knowledge about current care, gaps in care, and the natural history of the disease is forthcoming. Finally, results of research efforts in primary prevention of type 2 diabetes mellitus for adults and youth soon will be available. The increasing evidence base will challenge current treat-

¶The ADA currently recommends intensifying treatment on the basis of HbA_{1c} concentration <8%. However, the recommended target goal for HbA_{1c} concentration is <7%.

ment guidelines and ultimately improve the health of children with type 2 diabetes mellitus over their lifetimes.

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