AHA Scientific Statement

Cardiovascular Disease Risk Factors in Youth With Diabetes Mellitus

A Scientific Statement From the American Heart Association

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The rates of both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) are increasing in youth.[1] In the past 10 years, guidelines for the identification and management of cardiovascular disease (CVD) risk factors in youth with diabetes mellitus have been published by multiple professional organizations, including the American Diabetes Association (ADA),[2,3] the American Heart Association (AHA),[4,5] the American Academy of Pediatrics,[6] the International Society of Pediatric and Adolescent Diabetes (ISPAD),[7] and the Pediatric Cardiovascular Risk Reduction Initiative.[8] This scientific statement summarizes and interprets these guidelines and new developments in the field in the past decade and outlines future research and clinical needs to improve cardiovascular health and risk factor management in youth with diabetes mellitus. Additional goals for this statement are to increase awareness of CVD risk factors and their identification, prevention, and treatment and to improve cardiovascular health in youth with diabetes mellitus by encouraging advancement in research and clinical care, including understanding and implementing current CVD guidelines. Improving cardiovascular health in youth with diabetes mellitus has important public health implications; therefore, this statement aims to reach healthcare providers in diabetes mellitus, cardiology, and related fields. (Note: The sections within this scientific statement are organized by diabetes mellitus type, when possible, with brief summary statements concluding each section. Multiple definitions for CVD are used in the cited articles. Readers of this statement should include risk factors, surrogate markers, and end-organ damage under this umbrella term of CVD.)

Scope of Problem

Type 1 Diabetes Mellitus

Multiple studies document an increase of 2% to 5% annually in the incidence of T1DM worldwide.[9] The SEARCH for Diabetes in Youth (SEARCH) study estimated that there were 166 018 to 179 388 youth with T1DM in the United States in 2010.[1] Worldwide, rates of T1DM differ as a result of variation in the genetics of autoimmunity, exposure to environmental triggers, and healthcare infrastructure differences with a resultant spectrum of survival at diagnosis and subsequent life span.[9] The rapid and sustained increase in T1DM suggests an environmental cause or genetic-environmental interaction because genetic shifts in such a short time period are unlikely.

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The cause of T1DM is the subject of multiple ongoing studies with the shared goal of identifying targets for prevention.[10,11] A cure is likely still far in the future, barring dramatic scientific breakthroughs, underscoring the need to improve cardiovascular health for people with T1DM.

Two- to 10-fold increases in rates of coronary heart disease and death resulting from coronary heart disease in T1DM were reported in multiple studies involving adults.[12–16] Despite some improvement in CVD risk factors and mortality for people with T1DM, these rates remain higher than in the nondiabetic population.[17–19] Multiple CVD risk factors exist in T1DM, with glucose control commonly considered to be the critical factor accounting for increased risk compared with nondiabetics. Although data from epidemiologic studies on glucose control in T1DM and CVD are inconclusive,[20] the Diabetes Control and Complications Trial–Epidemiology of Diabetes Complications (DCCT/EDIC) trial reported a 57% reduction in CVD in the intensively managed compared with the conventional arm after 17 years of follow-up.[21] However, although renal outcomes have greatly improved in people with T1DM, CVD outcomes lag behind, arguing that unaddressed risk factors exist and require further study. In the general population, female individuals have lower CVD risk than male individuals. However, this protective effect of female sex is lost with T1DM; CVD risk in female individuals approaches that of male individuals.[17,22–24] CVD risk factor management in T1DM needs to be improved.

Type 2 Diabetes Mellitus

Before the 1990s, T2DM was rarely diagnosed in youth,[25] but increased rates now parallel the increasing rates of pediatric obesity.[26] Although rates of T2DM in youth have increased in recent decades, T2DM continues to be less common than T1DM. The SEARCH study estimated that there were between 20 203 and 22 820 youth with T2DM in the United States in 2010 compared with 166 018 to 179 388 with T1DM.[1] By 2050, the prevalence of T2DM in youth is estimated to be 30 111 to 84 131, constituting 10% to 15% of all diabetes mellitus in youth in the United States.[1] Among non-Hispanic black (NHB), Hispanic, Asian-Pacific Islander, American Indian, and Alaska Native populations, the proportion of youth with T2DM is higher than in non-Hispanic whites (NHWs).[1]

Data on outcomes for people diagnosed with T2DM in childhood are limited compared with T1DM. However, existing data suggest increased rates of vascular disease,[27] including CVD.[28] Data for adults with diabetes mellitus from the Framingham Heart Study indicate a reduction in all-cause mortality from 1950 to 2005, but mortality remains twice as high and CVD mortality 3 times higher compared with nondiabetics.[29] A recent study from Australia reports greater mortality, more complications, and worse CVD risk factors in youth-onset T2DM than T1DM despite similar glucose control and shorter diabetes mellitus duration.[30] Great concern exists about future outcomes for youth diagnosed with T2DM in childhood,[31] with healthy weight and CVD risk factor management as priorities.

Duration of diabetes mellitus is consistently and not unexpectedly a risk factor for diabetic complications in general and for CVD specifically. For example, a 20- or 30-year duration of T1DM confers an increased risk for CVD compared with a similarly aged and controlled patient who is recently diagnosed. Moreover, concern exists that the duration of T2DM diagnosed in childhood may translate into early development of diabetic complications, including CVD.[30,31]

Racial/Ethnic Disparities

Type 1 Diabetes Mellitus

Disparities can be defined as differences in frequency, treatment, or outcomes for the disease based on race or ethnicity. T1DM affects far more NHW children than any other racial/ethnic group,[32] likely because of genetic differences in autoimmunity. Among youth <10 years of age, almost all diabetes mellitus cases are T1DM, regardless of race/ethnicity.

Although T1DM is more common in NHWs, minority youth with T1DM are reported to have poorer glucose control, more diabetes mellitus–related complications, and higher mortality.[33,34] For example, the T1D Exchange found that more minority children have diabetic ketoacidosis, kidney disease, CVD risk factors, and diabetes mellitus–associated mortality[33] and that NHW race was significantly associated with lower hemoglobin A_{1c} (HbA_{1c}).[32] Specifically, only 14% of NHB participants currently meet the ADA's HbA_{1c} target compared with 34% and 28% in NHW and Hispanic participants, respectively.[35]

One potential contributor to the racial/ethnic disparities in T1DM is that NHW youth with T1DM report higher self-monitoring blood glucose checks per day, a behavior that predicts better diabetes mellitus control.[36] In addition, in the T1D Exchange, significantly fewer Hispanic and NHB children used insulin pumps compared with NHW children, with pump use in NHB youth being significantly less than in Hispanic youth.[38] Even in the groups with the highest education, socioeconomic status, and insurance, NHB youth still had lower pump use.[38] In addition, differences in insulin resistance (IR) are another possible factor. Danielson et al[39] showed that IR was significantly lower in NHW youth than in minority youth with T1DM.

Type 2 Diabetes Mellitus

Racial disparities in T2DM have similarities and differences compared with T1DM. The major difference is that minority youth are much more likely to develop T2DM. The incidence of T2DM is the highest among youth who are American Indian (25.3 and 49.4 per 100 000 per year for those 10–14 and 15–19 years of age, respectively), followed by NHB (22.3 and 19.4 per 100 000 per year), Asian/Pacific Islander (11.8 and 22.7 per 100 000 per year), and Hispanic (8.9 and 17.0 per 100 000 per year), and lowest (3.0 and 5.6 per 100 000 per year) among NHW.[40] Second, minority youth have higher rates of obesity, hypertension, dyslipidemia, and other metabolic syndrome components associated with T2DM[41] and have higher HbA_{1c}, more CVD risk factors, and higher rates of diabetic ketoacidosis.[42] In particular, NHB adolescents are more likely to have hypertension, arterial stiffness, and higher C-reactive protein,[42,43] all possible explanations for the higher rates of myocardial infarction and stroke seen in NHB adults.[44] Another report shows higher intramyocellular lipid in both NHB and Hispanic youth compared with NHW youth.[45]

However, the picture is complicated. Age, lipids, blood pressure (BP), and duration of T2DM were differently associated with arterial stiffness in each racial/ethnic group, implying

different mechanisms of cardiovascular risk.[42] In addition, despite high rates of T2DM and CVD, NHB youth have a lower prevalence of hypertriglyceridemia,[46–48] decreased insulin sensitivity, yet upregulated β-cell function relative to insulin sensitivity,[49] less visceral fat,[45,50,51] and less hepatic fat, with rates of hepatic fat highest in Hispanic male adolescents.[52,53] Finally, although few data exist on racial/ethnic differences in renal function in youth with T2DM, data in adults show that racial/ethnic minorities were more likely to have proteinuric diabetic kidney disease and less likely to have nonproteinuric diabetic kidney disease.[54]

Thus, diabetes mellitus disproportionately affects particular racial/ethnic groups in frequency, treatment, and outcomes. Further exploring potential mechanisms, including disparities in care and physiological variation, may contribute to preventing race/ethnicity–associated disparities and allow targeted treatments.

Overview of Current Guidelines

Multiple guidelines, with a variety of evidence or opinion-based strategies, exist that are relevant to achieving CVD risk reduction in youth with diabetes mellitus. These guidelines include an overarching document on pediatric CVD risk,[8] scientific statements related to specific risk factors,[6] management guidelines on diabetes mellitus in children,[3,7,55] and a guideline focusing specifically on dyslipidemia in pediatric diabetes mellitus.[2] In general, the published guidelines are consistent in that major targets for CVD risk reduction include glucose control, hypertension, and dyslipidemia; recommendations for these CVD risk factors are summarized in Table 1. However, approaches to risk factor reduction and target levels differ. One area of difference between guidelines is the use of pharmacotherapy in patients with low-density lipoprotein (LDL) cholesterol (LDL-c) of 100 to 130 mg/dL who are resistant to lifestyle counseling. A second area of guideline divergence concerns dyslipidemia screening and treatment recommendations for T1DM versus T2DM. The 2003 ADA statement "Management of Dyslipidemia in Children and Adolescents With Diabetes"[2] recommends screening for lipid disorders more frequently in T2DM than in T1DM. A somewhat more substantive difference is in the AHA statement "Cardiovascular Risk Reduction in High-Risk Pediatric Patients"[4] which considers T1DM to be a higher-risk condition than T2DM and therefore uses different treatment targets based on the risk tier designation. However, the more recent National Institutions of Health statement elevates T2DM to the same risk status as T1DM and may be considered to supersede the previous recommendation.[8] Emerging data from the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study and others[30] will inform future scientific statements and guidelines[60] and suggest accelerated risk in T2DM. Another place where guidelines diverge is around goals for HbA_{1c}, with the ADA setting age-specific targets of 8.5% (<6 years of age), 8% (6–12 years of age), and 7.5% (13–18 years of age),[56] whereas ISPAD recommends a target of <7.5% for all children with diabetes mellitus.[61]

Pediatric guidelines also address behavioral risk factors, including smoking, physical activity (PA), diet, and weight management. All guidelines recommend screening for cigarette smoke exposure and offering smoking cessation services. In the 2006 AHA statement on the management of high-risk pediatric patients, Kavey et al[4] recommended obtaining a parental smoking history at every visit and a patient smoking history starting at 10 years of age. Exercise is promoted in all guidelines. The ADA 2005 T1DM statement recommends 30 to 60 minutes of moderate PA per day. The 2006 AHA statement[4] recommends ≥1 h/d of active play and ≤2 h/d of screen time. All guidelines for care of the child with diabetes mellitus recommend following a healthy diet; none target poor diet as an independent CVD risk factor. Instead, dietary improvement is recommended for treatment of CVD risk factors (low saturated fat for high LDL-c, low salt for hypertension). A lower-carbohydrate diet is the recommendation for high triglyceride levels in several guidelines. Obesity is also recognized as a contributing factor to CVD risk in that treatment of obesity is recommended for children with both T1DM and T2DM who have hyperlipidemia or hypertension. IR is a fundamental physiological process underpinning T2DM and a component of T1DM; however, the optimal measurement methodology is not clear, and none of the guidelines make specific recommendations about testing for IR. Similarly, inflammation is not recommended as a specific screening metric or therapeutic target in pediatric diabetes mellitus guidelines, although it is recognized as an important pathophysiological process in atherosclerosis.

Adherence to these guidelines was assessed in several studies, although most publications focus primarily on glucose management and less on screening for secondary complications related to CVD risk reduction.[62] A study in the United Kingdom found 83.5% compliance with lipid screening with T1DM,[63] and another in children with T2DM found that only half of the patients had lipid testing.[64] In a survey by Gosden et al,[65] only 66% of patients had their BP checked yearly, and other CVD risk factors were not addressed. The SEARCH study reported self-assessed adherence to guidelines in 1514 participants.[66] Those investigators reported that BP was checked at most or all visits in the majority of patients (95%), that lipid screening was done in 88% of patients but less commonly in the older T2DM patients (69%), and that BP measurement, although more common than lipid screening, was also less frequent in this population. The ADA statement on transition of pediatric diabetes mellitus patients to adult care noted that pediatric providers tend to use general guidelines for screening and treatment of lipid disorders, whereas adult providers use diabetes mellitus–specific guidelines.[67]

Since publication of the pediatric guidelines, large epidemiological studies have reported the frequency and current management of CVD risk factors in youth with both T1DM and T2DM. These studies make it clear that elevated traditional CVD risk factors such as HbA_{1c}, BP, and cholesterol are common. Moreover, the epidemiological data suggest that few youth with diabetes mellitus receive BP- or lipid-lowering medications as recommended by the guidelines (Table 2). It is important to note that these data were published relatively soon after the various CVD in diabetes mellitus guidelines were issued and may not reflect current practice in pediatric diabetes mellitus. More recently, the T1D Exchange reported that 4.4% of youth had the clinical diagnosis of microalbuminuria, but only 36% were treated with angiotensin-converting enzyme/angiotensin receptor blocker therapy.[71] The past decade has seen progression in knowledge and awareness of

Table 1. Summary of Guideline Recommendations Relevant to Pediatric Diabetes Mellitus

Guideline by Topic	Who Should Be Screened	How to Screen	Action Cut Points	Recommended Action	Differences in Recommendations Between T1DM and T2DM
Glucose control					
AHA cardiovascular risk reduction in high-risk pediatric patients (2006)[4]	All	Frequent HbA_{1c}, per ADA guidelines	No diagnosis or age differences, goal >7%	Intensify glucose control	None
ADA (2013)[56]	All	HbA_{1c} every 3 mo	Age 0–6 y >8.5%; Age 6–12 y >8%; Age 13–19 y >7.5%	Intensify glucose control	None
ADA (2005)[3]	All	HbA_{1c}	Age 0–6 y >8.5% (and <7.5%); Age 6–12 y >8%; Age 13–19 y >7.5%	Intensify glucose control	N/A
ISPAD (2011)[7]	All	HbA_{1c} 4–6 times per y for younger children, 3–4 times per y in older children, 2–4 times per y in adolescents	All ages >7.5%	Intensify glucose control	None
Lipid abnormalities					
AHA cardiovascular risk reduction in high-risk pediatric patients (2006)[4]	Not specified	Fasting lipid profile	T1DM LDL >100 mg/dL; T2DM LDL >130 mg/dL	Step 1 diet* for 6 mo; statins if >10 y and LDL not at cut point despite 6 mo of lifestyle therapy	Lower LDL cut point in T1DM vs T2DM; T1DM is a tier 1 risk condition, T2DM is a tier 2 (lower risk)
			TG 150–400 mg/dL; TG >700–1000 mg/dL	Low-fat, low-simple-carbohydrate diet and weight loss if necessary; consider niacin or fibrate	T1DM is a tier 1 risk condition, T2DM is a tier 2 (lower risk)
ADA (2013)[56]	>2 y at time of diagnosis if there is a family history of early CVD; ≥10 y of no family history; if LDL is <100 mg/dL at screening, recheck every 5 y	Fasting lipid profile once glucose is controlled	LDL >100 mg/dL	Lifestyle change, step 2 diet, with <7% of calories from saturated fat and dietary cholesterol <200 mg/dL; statins: if child is without risk factors aside from T1DM and LDL >160 mg/dL despite lifestyle therapy; if child has additional risk factors (including family history of early CVD) and LDL >130 mg/dL despite 6 mo of lifestyle therapy; goal of therapy is <100 mg/dL	None (T2DM less well specified)
ADA T1DM (2005)[3]	>2 y at time of diagnosis if there is a family history of early CVD or high cholesterol (TC >240 mg/dL); if no family history, screen at puberty (age >12 y); repeat every 5 y	Fasting lipid profile, once glucose is controlled	LDL >100 mg/dL	LDL 100-129 mg/dL: maximize nonpharmacological treatment: optimize glucose control, reduce weight if necessary, increase exercise, and decrease dietary saturated fat. Role of statins is unclear. LDL 130–159 mg/dL: statins are recommended; LDL >160 mg/dL: statins are strongly recommended; medication target: LDL <100 mg/dL	N/A

(*Continued*)

Table 1. Continued

Guideline by Topic	Who Should Be Screened	How to Screen	Action Cut Points	Recommended Action	Differences in Recommendations Between T1DM and T2DM
Lipid abnormalities (continued)					
ADA management of dyslipidemia in children and adolescents with diabetes (2003)[2]	>2 y at time of diagnosis if there is a family history of early CVD or high cholesterol (TC >240 mg/dL); if no family history, screen at puberty (age >12 y); if normal, screen every 5 y in T1DM, every 2 y in T2DM	Fasting lipid profile, once glucose is controlled	LDL >100 mg/dL; TG >150 mg/dL; HDL <35 mg/dL	Repeat abnormal values; LDL 100–129mg/dL: maximize nonpharmacological treatment: optimize glucose control, reduce weight if necessary, increase exercise, and decrease dietary saturated fat; LDL 130–159 mg/dL: consider statins based on total cardiovascular risk picture; LDL >160 mg/dL: treat with statins; medication target: LDL <100 mg/dL	Lipid screening is more frequent (every 2 y) for T2DM than T1DM (every 5 y)
ISPAD (2011)[7]	≥2 y if there is a family history, otherwise >12 y		LDL >100 mg/dL	Lifestyle is main treatment; statins should be considered if LDL >100mg/dL although long-term safety is not known	
AAP (2008)[6]	≥2 y, repeated every 3–5 y if normal	Fasting lipid profile	LDL ≥130 mg/dL	Lifestyle for 6 mo; statins for children age ≥8 y of age if LDL ≥130 mg/dL despite 6 mo of lifestyle therapy; target LDL: 110–130 mg/dL	
AAP management of T2DM in children and adolescents (2013)[57]	T2DM	Fasting lipid profile once under glucose control, then every 2 y	LDL ≥130 mg/dL	Dietary advice by a dietician; follow diet <30% calories from fat, <7% calories from saturated fat, cholesterol intake <200 mg/d, and avoidance of *trans* fats; LDL measurements; weight loss efforts if necessary; if LDL ≥130 mg/dL: statins; LDL target: <100 mg/dL	N/A
			TG 150–600 mg/dL; TG ≥700 mg/dL	Low glycemic index diet; fibrates or niacin	N/A
NHLBI (2011)[58]	T1DM: all; T2DM: all; any age	Average of 2 FLPs	LDL ≥130 mg/dL; Age <10 y, TG ≥100 mg/dL; Age ≥10 y, TG ≥130 mg/dL	Lifestyle therapy: Begin with CHILD1. If insufficient response move to CHILD2-LDL for high LDL, CHILD2-TG for high TGs Statins: Age 10 y and LDL ≥160 mg/dL without other RF, ≥130 mg/dL with 2 additional moderate RF or family history; in the case of extremely high lipid levels, medications may be considered in children ages 8–10 y under the supervision of a lipid specialist	No distinction made between T1DM and T2DM with regard to risk or treatment of lipid disorders
Hypertension					
AHA cardiovascular risk reduction in high-risk pediatric patients (2006)[4]	All patients	BP taken with proper technique at every encounter	SBP or DBP >90th percentile for age, sex, and height percentile or >120/80 mm Hg, whichever is lower; SBP or DBP >95th percentile on 3 occasions	Lifestyle therapy for 6 mo. ACE inhibitor if SBP remains >95th percentile. Goal on medications is BP >130/80 mm Hg or >95th percentile, whichever is lower; medications per fourth report	ACE inhibitor recommended specifically for T1DM, medication choice for T2DM not specified

(*Continued*)

Table 1. Continued

Guideline by Topic	Who Should Be Screened	How to Screen	Action Cut Points	Recommended Action	Differences in Recommendations Between T1DM and T2DM
Hypertension (continued)					
AAP management of T2DM in children and adolescents (2013)[57]	All T2DM patients	Check BP at every visit	>95th percentile	Initial treatment lifestyle modification; ACE inhibitor if the BP remains >95th percentile	N/A
ADA (2013)[56]	All patients		>90th percentile for age, sex, and height percentiles, persistent on 3 separate measurements with proper technique; >95th percentile or 130/80 mm Hg, whichever is lower	Lifestyle first for 3–6 mo, then medication. Medications as first treatment. ACE inhibitor is first line	
ADA T1DM (2005)[3]	All T1DM	Check BP at every visit using standard techniques	>90th percentile for age, sex, and height percentiles, persistent on 3 separate measurements with proper technique; >95th percentile or 130/80 mm Hg, whichever is lower	Diet low in salt Increased physical activity; glucose control; ACE inhibitor if lifestyle therapy for 6 mo does not sufficiently lower BP	N/A
ISPAD (2011)[7]	T1DM: all; T2DM: all	At least yearly	>95th percentile for children, 130/80 mm Hg for adults	ACE inhibitors	
NHLBI (2011)[58]	T1DM: all; T2DM: all	Auscultative BP at every medical encounter	>90th percentile for age, sex, and height percentiles, persistent on 3 separate measurements with proper technique; >95th percentile or 120/80 mm Hg, whichever is lower	Diet low in salt Increased physical activity; glucose control; ACE inhibitor if lifestyle therapy for 6 mo does not sufficiently lower BP	
"The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents" (2004)[59]	T1DM: all; T2DM: all	Auscultative BP at every medical encounter	Prehypertension: 90th to <95th percentile or >120/80 mm Hg, whichever is lower	Lifestyle for any level of BP; consider pharmacotherapy even with prehypertension; pharmacotherapy with stage 1 and stage 2 hypertension; consider ACE or ARB as first-line pharmacotherapy	None
Obesity					
AHA cardiovascular risk reduction in high-risk pediatric patients (2006)[4]	T1DM and T2DM	Assess BMI at every encounter	T1DM ≥85th percentile; T2DM ≥90th percentile	Diet, weight follow-up every 2–4 wk for 6 mo; if unsuccessful in reaching target in 6 mo, refer to intensive weight management program	Lower BMI target for T1DM than T2DM (85th vs 90th percentile)

AAP indicates American Academy of Pediatrics; ACE angiotensin-converting enzyme; ADA, American Diabetes Association; AHA, American Heart Association; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CHILD1/CHILD2, Cardiovascular Health Integrated Lifestyle Diet; CVD, cardiovascular disease; DBP, diastolic blood pressure; FLP, fasting lipid profile; HDL, high-density lipoprotein; ISPAD, International Society for Pediatric and Adolescent Diabetes; LDL, low-density lipoprotein; N/A, not applicable; NHLBI, National Heart, Lung, and Blood Institute; RF, risk factor; SBP, systolic blood pressure; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TC, total cholesterol; and TG, triglycerides.

*Nutritionist training for step 1 diet, goal <30% of calories from fat, <7% of calories from saturated fat, cholesterol <200 mg/d, avoidance of *trans* fats.

CVD as an important issue in pediatric diabetes mellitus. The first set of guidelines has raised the awareness of CVD risk in youth with diabetes mellitus and descriptive data on rates of CVD risk factors. Reports of low rates of pharmacological treatment have followed. Increased implementation of clinical guidelines needs to be a priority among youth with diabetes

Table 2. Prevalence (%) of Hypertension and Dyslipidemia Diagnosis and Pharmacological Treatment

Study	Hypertension	Rx Treatment	Dyslipidemia	Rx Treatment
SEARCH[68,69]		1.5 total		1 total
T1DM (n=2165)	5.9		15	
T2DM (n=283)	23.7		24	
DPV[70]				
T1DM (n=27 358)	8.1	2.1	28.6	0.4

DPV indicates Diabetes Patientien Verlaufsdokumentation; Rx, prescription medication; T1DM, type 1 diabetes mellitus; and T2DM, type 2 diabetes mellitus.

mellitus. Evidence-based guidelines to promote greater consistency in the approaches to risk factor management and risk factor cut points will be critical to achieving this goal. Such guidelines can be achieved only by gaining a better understanding of the pathophysiology for CVD and risk factor progression in youth with diabetes mellitus.

Current Research

Data from a number of ongoing large, multicenter, observational and interventional research studies are referenced in this statement. Brief descriptions of these studies are provided in the online-only Data Supplement.

Target Organ Damage

The relationship between CVD risk factors and CVD events has been well described in the Framingham Heart Study.[72] Subjects from pediatric longitudinal studies have not aged sufficiently to have suffered CVD events, but the Bogalusa Heart Study,[73] Muscatine study,[74] and Cardiovascular Risk in Young Finn study[75] demonstrated tracking of risk factors from childhood to adulthood and a strong relationship between CVD risk factors measured in healthy children and markers of atherosclerosis, including carotid intima-media thickness (cIMT), measured in adulthood.[76] New evidence suggests that youth with diabetes mellitus can develop target organ damage starting in adolescence.

Echocardiography is recommended by both adult[77] and pediatric[58] guidelines for the evaluation of CVD risk factor–related target organ damage. The prevalence of left ventricular hypertrophy in adults with T2DM is high (23%).[78] Higher left ventricular mass in people with diabetes mellitus predicts decline in kidney[79,80] and cardiac[81,82] function and was an independent predictor of hard cardiovascular events in adults with T2DM.[83]

Similarly, Nadeau et al[84] found higher body size–indexed left ventricular mass in adolescents with T1DM compared with control subjects. Abnormal ambulatory BP patterns were also associated with higher left ventricular mass in youth with T1DM.[85] Diastolic dysfunction is also common in T1DM,[86] especially in youth with microvascular disease (microalbuminuria or retinopathy),[87] with a prevalence as high as 25%[88] correlated with glucose control.[89] Cardiac mass has also been found to be higher in adolescents with T2DM compared with control subjects[90] with concomitant abnormalities with diastolic filling.[91] Clearly, adverse cardiac changes are occurring in young patients with both T1DM and T2DM.

Adverse vascular changes such as higher aortic thickness[92] and cIMT have been found in adolescents with T1DM compared with control subjects.[93–97] Factors associated with this higher cIMT include lower vitamin C levels[98] and longer duration of disease.[99,100] Adolescents with T2DM also demonstrate higher cIMT compared with healthy control subjects,[101,102] with diabetes mellitus duration[103] and glucose control playing a role.[104] Factors affecting the progression of cIMT in adolescents and young adults with diabetes mellitus include the number of receptors for advanced glycation end products,[105] HbA_{1c},[106] and diabetes mellitus duration.[107] In adults, intensive diabetes mellitus treatment has slowed the progression of cIMT,[108] whereas in adolescents with T1DM (n=56), treatment with pentoxifylline, a hemorrheological agent available in Europe, led to regression of cIMT compared with placebo.[109]

Increased arterial stiffness, including lower abdominal aorta distensibility measured with ultrasound, was found in children with T1DM, although there was no association with diabetes mellitus duration or HbA_{1c}.[110] With the use of arterial tonometry, augmentation index, a measure that incorporates central arterial stiffness and wave reflections, and pulse-wave velocity, a measure of wave propagation, were found to be increased in children with T1DM.[93,94] Similar results were found in the larger SEARCH cardiovascular study (n=535), which found reduced brachial distensibility in youth with T1DM in addition to increased augmentation index and pulse-wave velocity.[111] Studies that found no increase in arterial stiffness in T1DM used nonstandard methods of assessing arterial stiffness that have not been validated in youth.[112,113] One large study of adolescents with T2DM (n=195) demonstrated increased arterial stiffness (lower brachial distensibility, higher augmentation index and pulse-wave velocity) in adolescents with T2DM compared with either lean or obese control subjects.[114] The only interventional study showed a trend for improvement in augmentation index with statin administration in youth with T1DM (n=51).[115]

Reduced brachial flow-mediated dilation has been found in very young (8.3±0.3 years) children with T1DM.[116] Endothelial dysfunction has been demonstrated in numerous studies in adolescents with T1DM.[96,117] Nonultrasound methods for assessing endothelial function, including peripheral arterial tonometry,[118,119] and laser flow Doppler studies[120] have demonstrated similar case-control differences. Poor endothelial function was associated with higher HbA_{1c}[121] and poor fitness level[122] but was not related to inflammation.[123] Endothelial dysfunction has also been found in youth with T2DM when measured by flow-mediated dilation[101] venous plethysmography.[124] Interventions including exercise[125] and intensive glucose control[126] improved endothelial function in young patients with T1DM. Collectively, these studies suggest significant cardiovascular compromise in youth with both T1DM and T2DM at a young age.

Peripheral neuropathy is another form of target organ damage found in young adults with diabetes mellitus.[127] Children with T1DM may already have abnormal nerve conduction at the time of diagnosis.[128] Heart rate variability analysis has emerged as a useful tool to assess autonomic tone, and studies in youth with diabetes mellitus have demonstrated a reduction in heart rate variability,[129] mostly with vagal withdrawal early[130] and sympathetic dysfunction later in the disease

process.[131] However, 1 large study (n=354) found overall heart rate variability reduction, suggesting a more advanced state of cardiac autonomic neuropathy.[132] Predictors of abnormal heart rate variability in children with T1DM included higher HbA_{1c}[132] and low PA.[133] The few small studies of neurological function conducted in youth with T2DM showed lower cognitive function,[134] peripheral neuropathy,[135] and lower heart rate variability compared with control subjects.[136] These early changes in neurological function have implications for future CVD because autonomic dysfunction measured in childhood predicts increased arterial stiffness 18 years later.[137]

Retinopathy is a microvascular complication of long-standing diabetes mellitus[138] that is associated with cognitive decline in adults.[139] Estimates of the incidence of retinopathy in youth with T1DM vary from 9%[140] to ≈15% per 100 person-years.[141,142] There are limited data in youth with adolescents with T2DM, but these data suggest similar retinal abnormalities are developing.[143,144] Factors influencing retinopathy in children with T1DM include vitamin D deficiency,[145] BP,[146] duration of disease,[147] and glucose control.[148,149] The prevalence appears to be declining in both children[150] and adults,[138] possibly related to more intensive treatment.[151]

In summary, target organ damage can be identified in adolescents with both T1DM and T2DM that is related to cardiovascular risk factors, duration of disease, and glucose control. Providers should follow the Pediatric Cardiovascular Risk Reduction Initiative recommendation on echocardiography in youth with hypertension that advocates echocardiography to rule out left ventricular hypertrophy before the initiation of antihypertensive therapy with the caveat that the goal for BP in diabetics is lower (the 90th percentile) compared with a non-diabetic population (the 95th percentile).[58] There is insufficient evidence to recommend other methods of imaging or testing for target organ damage for the prevention of CVD in youth with diabetes mellitus.

CVD Risk Factors

One approach to CVD risk reduction in diabetes mellitus uses the A, B, C approach. In addition to glucose control (HbA_{1c}, or A), blood pressure (BP or B) and cholesterol (C) management are emphasized.[56] Other modifiable CVD risk factors for people with diabetes mellitus include obesity, IR, inflammation, oxidative stress, kidney disease, and lifestyle factors such as smoking, diet, exercise, psychosocial stress, depression, and sleep. Nonmodifiable CVD risk factors include genetics, family history, diabetes mellitus duration, and racial/ethnic disparities.

Glucose Control

Glucose control is the cornerstone of diabetes mellitus management. The current ADA and ISPAD HbA_{1c} goals for children and adolescents are listed in Table 1.[55,61] These glucose goals have been extrapolated from adult studies that have shown that reduction of HbA_{1c} to ≈7% reduces microvascular complications (neuropathy, nephropathy, and retinopathy) in T1DM and T2DM.[34,151a] However, data on the relationship between HbA_{1c} and cardiovascular complications are weaker because large clinical trials and epidemiological cohort studies in adults have had conflicting results and long-term studies in children are lacking.

Type 1 Diabetes Mellitus

The DCCT and follow-up EDIC cohorts have shown that glycemic lowering, even for a few years, reduces the future rate of myocardial infarction, stroke, and CVD death.[21,34,153] Several large, prospective, observational cohort studies, including the EDC,[154] the EURODIAB Prospective Complications Study (EURODIAB),[155] and the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR),[156] have failed to demonstrate similar results. Possible explanations for the discrepancies between studies are that the DCCT/EDIC cohort initiated intensive insulin therapy early in a population with a relatively short duration of diabetes mellitus, the cohort had a low prevalence of IR and renal disease (both strong predictors of coronary artery disease), and the intensive insulin treatment arm achieved a remarkably low mean HbA_{1c} of 7.4%.[20] Thus, the relationship between lowering of HbA_{1c} and reduction of cardiovascular events likely exists but only in a cohort at low risk for coronary artery disease with a short duration of diabetes mellitus when tight glucose control is achieved early. Such an interpretation emphasizes the importance of glucose control in youth.

Data addressing cardiovascular events are currently unavailable in the pediatric age group. Thus, studies evaluating the relationship between HbA_{1c} and CVD outcomes in youth have relied on noninvasive imaging modalities to assess the early vasculature changes.[157] In adolescents (mean age, 18.1±3.1 years), Krantz et al[158] found no relationship between HbA_{1c} and cIMT. Similarly, Haller et al[159] also found no association between HbA_{1c} and augmentation index measured by radial tonometry (age range, 10–18 years). Wadwa et al[160] noted a univariate association between HbA_{1c} and pulse-wave velocity but not after adjusting for other risk factors. These cross-sectional data in youth with T1DM emphasize that longitudinal studies are needed because the effects of glucose control on CVD outcomes did not manifest until 17 years of follow-up in the DCCT/EDIC study.

Type 2 Diabetes Mellitus

Similar to T1DM, data from the UK Prospective Diabetes Study (UKPDS)[151a,161] and its 10-year cohort follow-up[163,164] suggest that intensive glucose control may be of greater CVD benefit when initiated early in T2DM. Conflicting results have been seen in more recent clinical trials in older adults with more advanced CVD.[165–167] In fact, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which aimed to achieve an HbA_{1c} of <6% in adults with a known cardiovascular event or major CVD risk factor, was halted because of the finding of increased mortality in the intensive treatment arm.[168]

Only a few studies in adolescents with T2DM have evaluated the association between HbA_{1c} and early vascular changes. Wadwa et al[160] studied 60 adolescents (mean age, 17.4±2.7 years) with a median duration of diabetes mellitus of 3.1 years (range, 2.1–4.5 years) and found no relationship between HbA_{1c} and arterial stiffness. In contrast, using cIMT, Shah et al[169] demonstrated an independent association with HbA_{1c} in 129 adolescents (mean age, 18.9±3.2 years) such that each 1% increase in HbA_{1c} was associated with a 30% increase in the odds for a thicker carotid artery. Similarly, Kotb et al[103] found a univariate association between HbA_{1c} and cIMT in youth 12 to 19 years of age. These cross-sectional

studies in T2DM youth suggest that glucose control is associated with increased arterial thickness but not stiffness.

In summary, it is important to note that although the data from older adults suggest a minimal effect of intensive HbA_{1c} lowering on CVD, this should not be extrapolated to imply no future benefit in pediatric diabetes mellitus. Instead, what long-term follow-up of the DCCT/EDIC and UKPDS cohorts suggests is that improved glucose control, when initiated early in young people, leads to a reduction in cardiovascular events. This is of crucial importance in the pediatric population, in which improved glucose control has the potential to alter future CVD risk. Additionally, given the known benefits of lowering HbA_{1c} on microvascular complications, clinicians should emphasize the long-term benefits of tight glucose control in children and adolescents with diabetes mellitus.

Blood Pressure

The prevalence of clinic hypertension in youth with T1DM (4%–7%)[170,171] and T2DM (25%–40%)[68,172,173] is higher than in healthy children. Abnormal ambulatory BP patterns[174,175] such as reduced nocturnal dipping[176] may also be identified. Higher BP levels predispose to the development of microalbuminuria,[177] nephropathy,[178] retinopathy,[146] and carotid thickening.[179,180] The determinants of BP levels in children with diabetes mellitus include poor diet,[181] adiposity,[182,183] diabetes mellitus–related autonomic imbalance,[130,184] and poor glucose control.[185,186]

Adult guidelines set the goal for BP in people with diabetes mellitus to ≤130/80 mm Hg on the basis of longitudinal studies with hard cardiovascular events as outcome.[77] Lowering BP further may improve target organ measures (cIMT, left ventricular mass, proteinuria),[187,188] but the risk of a drop in diastolic BP to <60 mm Hg,[189] a level that may impair coronary filling, has led the ADA to suggest avoiding hypotension.[56] No pediatric longitudinal studies with hard cardiovascular events are available; however, evidence for target organ damage in youth with diabetes mellitus[102,114,190] led to the recognition that children with either T1DM or T2DM are at elevated risk of developing atherosclerotic CVD before 30 years of age.[58] Therefore, reducing BP to the ≤90th percentile for age, sex, and height or ≤120/80 mm Hg at any age was recommended.[58] Although these recommendations were based on inferences gained from cross-sectional studies, observational studies, and adult data (grade D, expert opinion), the American Academy of Pediatrics endorses the goal of BP ≤90th percentile in pediatric diabetes mellitus.[57] In summary, the recent Pediatric Cardiovascular Risk Reduction Initiative recommendation for screening for and treatment of hypertension in youth with diabetes mellitus provides comprehensive guidance.[58]

Cholesterol

Elevated LDL-c is firmly established by genetic, epidemiological, and animal studies as a major contributing risk factor to CVD.[191–197] Therefore, LDL-c is the primary target for lipid health in children and adolescents.[198] In the SEARCH study, the prevalence of an elevated LDL-c (>130 mg/dL) is 15% and 24% in youth with T1DM and T2DM, respectively.[69] LDL-c lowering reduces cardiovascular events in adults with T2DM[199] and improves subclinical atherosclerosis in children with familial hypercholesterolemia.[200,201] Collectively, these data suggest that LDL-c lowering may attenuate the risk for atherosclerosis in youth with diabetes mellitus.

Type 1 Diabetes Mellitus

Limited longitudinal prospective studies are available on cholesterol management in youth with diabetes mellitus. For T1DM, longitudinal prospective studies of at least 2 years' duration and involving between 46 and 1100 patients demonstrate that worse glucose control (increased HbA_{1c}) is associated with increased LDL-c (or the highly correlated non–high-density lipoprotein [HDL] cholesterol)[202–207] and demonstrate an increase in LDL-c with increasing body mass index (BMI) or BMI *z* score.[203,204,206] In addition, a large cross-sectional study of ≈29 000 German and Austrian patients with T1DM demonstrated strong associations between LDL-c and HbA_{1c} and between LDL-c and BMI.[208] From these data, it is clear that lower LDL-c levels can be achieved by improved glucose control and reduced BMI in addition to a healthy diet.

Type 2 Diabetes Mellitus

Few studies address hyperlipidemias in pediatric T2DM. A longitudinal study demonstrated increased LDL-c with worse glucose control,[209] and a cross-sectional study reported higher LDL-c levels in patients with higher mean HbA_{1c} and BMI *z* scores.[28] Data from the TODAY study suggest that behavioral intervention and glucose control will not be sufficient to achieve lipid goals in adolescents with T2DM.[210] Importantly, in T2DM and potentially T1DM, the high levels of insulin that result from IR cause hyperlipidemia by selectively stimulating lipoprotein production via the liver transcription factor sterol regulatory element binding protein 1c.[211] Therefore, therapies that reduce IR (including PA, weight reduction, and metformin) can reduce hyperlipidemia. Reducing IR will also improve HDL cholesterol and triglyceride levels, which frequently are abnormal in T2DM.[69]

Treatment

The questions remain whether the LDL-c lowering achieved with nonpharmacological interventions is sufficient to prevent atherosclerosis or to achieve lipid goals,[202,206] at precisely what age LDL-c reduction should begin,[212] and what the ideal LDL-c treatment goal should be. The association of HbA_{1c} and BMI change with lipids was positive but may be insufficient to achieve lipid goals on the basis of observational data from the SEARCH study in T1DM youth,[206] similar to the TODAY data in T2DM youth.[210] Although statins are considered safe and well tolerated in adults, long-term safety studies that follow up children into adulthood are lacking. The AHA statement on drug therapy cautions that statin use in adolescence needs to be studied further to determine the impact on psychological and intellectual development.[5] Animal studies raise concerns about potential untoward effects of statins on the rapidly developing central nervous system (eg, impaired myelin formation).[213,214] However, many statins do not cross the blood-brain barrier, data in adults suggest no harmful central nervous system effects,[215–217] and randomized, placebo-controlled studies of statins in children with familial hyperlipidemia have not demonstrated adverse effects in growth or development.[8] It is important to be aware of the teratogenicity of statins when prescribing

them for female patients of childbearing age.[5] Some adult studies have shown regression of coronary atherosclerosis assessed by angioplasty or carotid ultrasound. Therefore, it may be possible to reduce existing atherosclerotic disease with intensive lipid-lowering therapy at an older age.[218,219] The pros and cons of pharmacological treatment of dyslipidemia in adolescents with diabetes mellitus are reviewed elsewhere.[212,220]

In summary, LDL-c levels >130 mg/dL in T1DM and T2DM warrant interventions to reduce LDL-c levels by improving glucose control, decreasing IR (BMI reduction, healthy diet, and increased PA), and, in postpubertal children, considering the addition of a pharmacological agent.

Obesity

Type 1 Diabetes Mellitus

Compared with those with T2DM, fewer children and adolescents with T1DM are overweight or obese. However, in the SEARCH study, ≈22% of the children and adolescents with T1DM were overweight, and this percentage was higher than youth without diabetes mellitus in the National Health and Nutrition Examination Survey (NHANES) cohort (≈16%).[221] The prevalence of obesity in youth with T1DM in this study was ≈12.6%. Emerging evidence suggests that higher doses of insulin used to improve glucose control are associated with greater increases in BMI over time.[222]

Drawing from the adult literature, it is clear that intensive treatment aimed at improving glucose control is associated with weight gain and worsening of the cardiovascular risk factor profile among patients with T1DM. Data from the DCCT demonstrated that subjects in the top quartile of weight gain had the highest BMI, waist-to-hip ratio, BP, and proatherogenic lipoprotein level.[223] The only distinguishing factor at baseline between these patients and those in the lower quartiles of weight gain was higher HbA_{1c}, suggesting that the intensity of treatment was likely responsible for the increase in central adiposity and deterioration of the CVD risk factors. Moreover, in the EDIC follow-up study, those who were in the top quartile of BMI change in the intensively treated arm had greater cIMT and tended to have higher coronary artery calcification scores compared with those in the lower BMI change quartiles.[224] Together, these data suggest that more intensive glucose control, likely achieved with higher insulin use, is associated with progressive worsening of CVD risk factors and subclinical atherosclerosis among those in the highest quartile of BMI increase.

Type 2 Diabetes Mellitus

Results from the SEARCH study suggest that ≈80% of youth with T2DM are obese (≈10% are overweight).[221] Obesity is a pathogenetic factor contributing to the development of T2DM among children and adolescents, likely through its association with IR, one of the primary pathophysiological processes underlying the disease. Therefore, in addition to achieving optimal glucose control, managing obesity should be a primary consideration in the treatment strategy for pediatric T2DM. Unfortunately, many drugs used to treat hyperglycemia are associated with weight gain (insulin, thiazolidinediones, and sulfonylureas). Indeed, treatment with rosiglitazone in the TODAY study was associated with increasing BMI and body fat.[60] Results of the TODAY study further suggest that weight loss is extremely difficult for pediatric patients with T2DM. Despite relatively intensive lifestyle modification/behavioral counseling and metformin offered throughout the study, mean BMI and body fat increased in all 3 treatment arms.[60]

Ideally, medications used to treat pediatric T2DM should be associated with weight loss or at least should have a weight-neutral effect. According to recent guidelines from the American Academy of Pediatrics,[225] metformin should be the first-line therapy for the treatment of pediatric T2DM. In general, metformin is associated with modest weight loss. Three randomized, placebo-controlled trials conducted in obese youth without diabetes mellitus reported a BMI reduction of ≈3% over a treatment period of 6 to 12 months.[226–228] Neither glucagon-like peptide-1 receptor agonists nor dipeptidyl peptidase-4 inhibitors are currently approved by the US Food and Drug Administration for the treatment of T2DM in children and adolescents. However, if the safety and efficacy of these drug classes are established and US Food and Drug Administration approval is obtained, these medications may be an attractive option because glucagon-like peptide-1 receptor agonists are associated with weight loss and dipeptidyl peptidase-4 inhibitors appear to be weight neutral, although safety concerns about long-term treatment exist that are based on recent autopsy studies.[229] Two relatively small clinical trials have demonstrated that exenatide, a glucagon-like peptide-1 receptor agonist, reduces BMI by ≈3% to 4% in severely obese adolescents without diabetes mellitus.[230,231]

Although typically reserved for severely obese adolescents with significant comorbidities, bariatric surgery has been shown to be far superior to lifestyle modification therapy or pharmacotherapy in terms of BMI reduction[232–234] and may be an effective treatment option for severely obese teens with T2DM. Beyond weight reduction, improved glucose control appears to be an important benefit of bariatric surgery among patients with T2DM. Indeed, a recent study in adults with T2DM demonstrated that compared with those treated with medical management alone, patients who underwent Roux-en-Y gastric bypass required on average 3 fewer medications for glucose control.[235] In youth with T2DM, Roux-en-Y gastric bypass led to remission of the T2DM in 10 of the 11 participants, with significant improvements in BMI (−34%), fasting blood glucose (−41%), fasting insulin concentrations (−81%), HbA_{1c} levels (7.3%–5.6%), IR, serum lipid levels, and BP.[236] However, much more information about the long-term safety and efficacy of surgical management is be needed before recommendations can be offered on the use of bariatric surgery for the treatment of obesity and T2DM among adolescents.

In summary, obesity increases CVD risk in both T1DM and T2DM, and a direct parallel can be drawn between T2DM and T1DM in terms of treatment approaches aimed at reducing obesity (T2DM) and preventing obesity (T1DM).

Insulin Resistance

IR predicts cardiovascular morbidity and mortality in the metabolic syndrome and T2DM.[237–239] IR is best measured by the hyperinsulinemic-euglycemic clamp using the glucose disposal rate (GDR), especially in diabetes mellitus, in which β-cell dysfunction disrupts estimates based on fasting insulin. However, clamp studies are difficult to perform. Therefore, non–insulin-based estimates were recently created with the use of surrogate

clinical measures.[240,241] The presence of pathological IR in youth is concerning because early onset translates to long exposure of the cardiovascular system to its negative effects.

Type 1 Diabetes Mellitus

IR is increasingly recognized as a key factor in T1DM.[84] Normal-weight adolescents with T1DM have significantly lower GDR than control subjects[84,242] matched for BMI, pubertal stage, and activity level[84] and were as insulin resistant as obese nondiabetic youth.[84] Importantly, IR (low GDR) is associated with a more atherogenic fasting lipid profile and lipoprotein subfraction cholesterol distribution and decreased cardiopulmonary fitness and vascular reactivity.[84,243–245] Although long-term data linking IR in T1DM youth to negative long-term cardiovascular outcomes in T1DM adults are lacking, IR correlates with coronary artery calcification,[246] coronary artery disease, and actual cardiovascular events.[154,247] These data argue that IR in T1DM has effects on the cardiovascular system similar to those seen in T2DM.

Despite the significant IR reported in T1DM, the phenotype of IR is unique in that individuals with T1DM typically lack the metabolic syndrome features characteristic of T2DM. For example, compared with individuals with T2DM or obese and normal-weight control subjects, youth with T1DM had lower intrahepatic, visceral, and intramyocelluar fat, BP, and triglycerides and higher HDL and adiponectin than expected.[84,244,245] Also unexpectedly, intra-abdominal fat volume did not correlate with IR in adult women with T1DM.[248] Thus, the mechanisms of IR likely differ between T1DM and T2DM, requiring further research to customize treatment strategies. Furthermore, obesity is now common in youth with T1DM (40% of adolescents with T1DM in the large multicenter T1D Exchange Network were overweight or obese),[35] likely further worsening IR and CVD, because obesity in adults with T1DM predicts coronary artery calcification progression, independently of dyslipidemia, hypertension, and inflammation.[249] Accordingly, direct prevention and treatment of IR are now priorities in T1DM research.

Type 2 Diabetes Mellitus

IR is present from the early stages of T2DM. Adolescents with T2DM are more insulin resistant than obese adolescents matched for BMI, Tanner stage, and PA level.[250] Urbina et al[251] found that arterial stiffness, as measured by brachial artery distensibility and pulse-wave velocity, was associated with HOMA (homeostasis model assessment)-assessed IR in adolescents and young adults with T2DM, although not independently of age, sex, BMI, and BP. Similarly, Kotb et al[103] found that cIMT was higher in adolescents with T2DM than in control subjects and correlated with HOMA-assessed IR. Nadeau et al[250] reported reduced cardiopulmonary fitness in adolescents with T2DM compared with lean and obese adolescents, and this reduction in $\dot{V}o_2$ peak was strongly and independently correlated with GDR. Furthermore, Cerutti et al[252] determined that adolescents with T2DM had reduced vagal but increased sympathetic indexes, indicating autonomic dysfunction, which correlated with oral glucose tolerance test–derived IR. Perez-Mendez et al[253] found that HDL cholesterol size distribution was shifted toward smaller particles in pediatric T2DM patients and that HOMA-derived IR was the main factor associated with these HDL size abnormalities.

Given the association between IR and CVD risk factors in T2DM, treatment aimed at improving IR is critical. Metformin (HOMA),[254] thiazolidinediones (GDR),[60,255,256] structured exercise independent of weight change (GDR),[257,258] and weight loss (GDR and hepatic IR)[259,260] are all reported to improve IR in youth with T2DM or obesity. In particular, the drastic weight loss seen with gastric bypass has resulted in T2DM remission and improvements in IR (fasting insulin, ratio of triglycerides to HDL), β-cell function, and cardiovascular risk factors in adolescents and adults with T2DM.[236,261] In addition, IR (assessed by steady-state plasma glucose) was the sole independent predictor of endothelial dysfunction in adults with T2DM as assessed by flow-mediated dilation, and pioglitazone treatment improved endothelial function, which significantly correlated with improved IR.[262]

In summary, mechanisms underlying IR in T1DM and T2DM may differ, and new methods to improve IR in pediatric diabetes mellitus are critically needed.

Inflammation

Type 1 Diabetes Mellitus

Although inflammation has been implicated in the pathogenesis of T1DM,[263,264] many studies have sought to examine whether inflammation is associated with CVD risk factors. In the SEARCH study, children and adolescents with T1DM had higher levels of interleukin-6 and fibrinogen compared with normal-weight subjects.[265] In addition, C-reactive protein was higher in patients with diabetes mellitus in the top 3 quartiles of HbA_{1c}. Other studies have reported that T1DM is associated with elevated C-reactive protein[266] and monocyte chemoattractant protein-1.[267] Acute hyperglycemia, poorer glucose control, and dysregulated adipocyte function may be some of the mechanisms involved in the higher levels of inflammation observed in pediatric T1DM.[244,245,268]

Type 2 Diabetes Mellitus

Adolescents with T2DM had higher levels of C-reactive protein and interleukin-6 compared with obese adolescents without diabetes mellitus and normal-weight controls.[250] Two studies demonstrated that children and adolescents with T2DM had higher levels of C-reactive protein compared with normal-weight control subjects but that levels were not significantly higher than those among obese youth without diabetes mellitus.[102,114] In a study of obese First Nation youth with and without T2DM, there was no difference between groups for tumor necrosis factor-α or C-reactive protein; however, interleukin-6 levels were higher in those with T2DM compared with those without diabetes mellitus.[271]

From current evidence, it appears that inflammation is elevated in the context of pediatric T2DM but that levels are not consistently higher than those found in obese youth without diabetes mellitus. It will be important for future studies to evaluate the impact of various diabetes mellitus treatments on inflammatory cytokines. Indeed, studies in adults have demonstrated that thiazolidinediones, metformin, and glucagon-like peptide-1 receptor agonists can reduce inflammation.[272–276]

Oxidative Stress

Type 1 Diabetes Mellitus

Oxidative stress is thought to be a primary mechanism involved in atherogenesis. Within the context of diabetes mellitus, chronic hyperglycemia and acute hyperglycemia produce free radicals and thereby increase levels of oxidative stress.[277] Most[278–285] but not all[286] studies report that oxidative stress levels are higher in youth with T1DM compared with healthy control subjects. Consistent with the hypothesis that uncontrolled hyperglycemia is one of the primary mechanisms responsible for oxidative stress in diabetes mellitus, multiple studies have suggested that levels of oxidative stress tend to be higher at diagnosis and subsequently decrease over time as glucose control is established.[282–285,287] Evidence suggests that oxidative stress in pediatric T1DM is associated with inflammation, endothelial activation, and other early signs of vascular dysfunction.[98,288,289,291] Although intervention studies are few, 1 study reported that vitamin E supplementation reduced levels of oxidative stress among children with T1DM.[292]

Type 2 Diabetes Mellitus

Despite the important implications in relation to CVD risk, little is known about oxidative stress in pediatric T2DM. One study compared levels of antioxidants and markers of oxidative stress among 3 groups: adolescents with T2DM, obese control subjects without diabetes mellitus, and normal-weight control subjects.[271] Although antioxidant status did not differ among the groups, levels of oxidized LDL-c were higher in those with T2DM compared with the normal-weight control subjects but were not different from levels in the obese control subjects without diabetes mellitus, suggesting that oxidative stress was associated with obesity and not diabetes mellitus per se.

Kidney Function

Renal disease in youth with diabetes mellitus differs significantly between patients with T1DM and T2DM. Development of diabetic nephropathy in T1DM classically takes 10 to 15 or more years to manifest clinically, although clinically silent changes such as glomerular hyperfiltration and ultrastructural abnormalities may be present for years before overt nephropathy can be demonstrated. On the other hand, renal manifestations can almost always be demonstrated at the time of diagnosis in patients with T2DM, which reflects the years of obesity-related metabolic and hemodynamic abnormalities these patients have experienced before becoming symptomatic from their diabetes mellitus.[293]

Type 1 Diabetes Mellitus

In a group of children enrolled in the Oxford Regional Prospective Study,[294] glomerular hyperfiltration was associated with both the advent of puberty and the development of microalbuminuria independently of glucose control. However, in a study of young adults from the First Joslin Kidney Study,[295] renal hyperfiltration did not appear to affect the development of microalbuminuria over 15 years of follow-up. Most recently, a study conducted in Finnish adults demonstrated that the incidence of hyperfiltration was similar in adults with T1DM compared with the general population and that patients with T1DM with higher estimated glomerular filtration rate were not more likely to develop microalbuminuria than those with normal glomerular filtration rate.[296] Taken together, these results suggest that hyperfiltration may be more important at younger ages. Thus, children with T1DM who manifest hyperfiltration may be at increased risk of developing microalbuminuria, whereas this may not be the case for adults.

On the other hand, renal structural changes develop early in T1DM, even in children, and are correlated with the development of microalbuminuria and systemic hypertension.[297] Renal biopsies performed in patients aged 10 to 40 years of age enrolled in the International Diabetic Nephropathy Study[298] showed that thickening of the glomerular basement membrane and increased mesangial matrix could be demonstrated after just 2 to 8 years of T1DM and that these abnormalities correlated with diastolic BP and duration of diabetes mellitus. Follow-up of this cohort demonstrated a correlation between the basement membrane changes and microalbuminuria, as well as a potential association with increased glomerular filtration rate.[299] A more recent biopsy study[300] confirmed that thicker glomerular basement membranes, poorer glucose control, and higher BP were significant predictors of microalbuminuria on long-term follow-up. Noninvasive markers of renal structural damage in T1DM that could help determine the optimal time to initiate renoprotective treatment are still needed at this time.

Type 2 Diabetes Mellitus

Several studies have demonstrated a 2- to 3-fold higher prevalence of microalbuminuria and macroalbuminuria in youth with T2DM compared with youth with T1DM,[301,302] as well as other features of diabetic nephropathy such as hypertension. In the TODAY study,[172] ≈13% of youth had microalbuminuria; even more alarmingly, nearly 40% had elevated BP. In Pima Indian youth with T2DM, microalbuminuria was common, affecting 18.5%, and predicted the development of macroalbuminuria.[303] However, in another study conducted in First Nation youth with T2DM,[304] ≈50% had intermittent microalbuminuria; within a subgroup of patients with persistent macroalbuminuria who had renal biopsies performed, most had evidence of immune complex deposition, suggesting that microalbuminuria in pediatric patients with T2DM is not always purely diabetes mellitus related.

In adults, it is well established that the metabolic abnormalities characteristic of obesity precede the development of symptomatic T2DM.[293] A similar pathophysiology likely precedes the development of T2DM in pediatric patients. Numerous studies have shown that abnormal BP can be demonstrated early in the course of T2DM in children. Elevated BP is common in obese adolescents,[305] and abnormalities of ambulatory BP are associated with abnormal metabolic factors.[306] In both the TODAY[172] and the SEARCH[68] studies, hypertension was common and was more frequent with increasing BMI. In another study using ambulatory BP monitoring,[307] abnormal BP patterns and microalbuminuria were both common in minority youth with relatively recently diagnosed T2DM. Thus, it appears that in T2DM long-standing metabolic abnormalities associated with obesity result in the development of both renal and cardiovascular manifestations suggestive of early diabetic nephropathy, even in adolescents.

There is controversy as to whether microalbuminuria is solely a marker of kidney disease. Microalbuminuria can remit and progress and may represent vascular damage in some patients or renal damage in others. Youth with diabetes mellitus are clearly a high-risk population who should be screened for renal disease and treated aggressively to prevent future CVD.

Smoking

In a study of Egyptian adolescents with T1DM, 50% of cigarette smokers had evidence of coronary artery calcification compared with 9.1% of nonsmokers ($P<0.001$).[308] Cigarette smoking in youth with T1DM also contributes to CVD risk through worsening glucose control, lipid profile, and endothelial function.[309] In the most comprehensive study of tobacco use among youth with diabetes mellitus, the SEARCH study found that the prevalence of cigarette smoking increased with age.[310] Among youth with T1DM who were 10 to 14, 15 to 19, and ≥ 20 years of age, the prevalence of smoking was 2.7%, 17.1%, and 34.0%, respectively.[310] In youth with T2DM who were 10 to 14, 15 to 19, and ≥20 years of age, the prevalence was 5.5%, 16.4%, and 40.3%, respectively.[310] Smoking among youth with either T1DM or T2DM was more common among those living in households with family annual incomes of ≤$50 000, suggesting the impact of socioeconomic status on the adaptation of smoking habits. Past and current smokers with T1DM had a higher prevalence of high triglyceride levels, high LDL levels, low HDL, and physical inactivity compared with the nonsmokers.[310] Similar associations were noted for youth with T2DM; however, likely because of the small sample size and number of cigarette smokers, the results did not reach statistical significance with the exception of high triglyceride levels. Smoking appears to increase CVD risk directly (eg, worsening endothelial function) and through its association with behavioral risk factors (eg, physical inactivity). The SEARCH study noted that <50% of youth 10 to 14 years of age reported being counseled by their healthcare provider about starting or stopping cigarette smoking.[310] Despite the health consequences associated with smoking, there appear to be no intervention trials in youth with diabetes mellitus designed to promote the avoidance of smoking. Strategies used by healthcare providers may include office-based screening and counseling methods, strategies to promote the use of these methods, and resources to help maintain cigarette avoidance between office visits.[312]

Diet

Numerous studies suggest that nutrition influences CVD risk.[193,313,314] Medical nutrition therapy guidelines have been shown to improve CVD risk factors in adults with diabetes mellitus[314,316]; however, studies evaluating the influence of specific dietary macronutrient content and eating patterns have yielded inconclusive results.[317] Observational and comparative studies among youth suggest that CVD risk may be influenced by diet composition, family cohesion, eating behaviors, and knowledge of and adherence to dietary recommendations.

The ADA guidelines for medical nutrition therapy do not recommend a specific distribution of macronutrient content in the diet. These guidelines are highly individualized, with recommendations that the combination of carbohydrates, protein, and fat be adjusted to meet glucose, BP, and lipid goals.[56] Additionally, these guidelines recommend that the intake of saturated fat should be <7% of total calories.[56] ISPAD recommends that the total daily distribution of energy intake in youth with diabetes mellitus includes a diet of carbohydrate (50%–55%), fats (30%–35%), and protein (10%–15%), with saturated fats and *trans* fatty acids making up <10% of total fat calories. These guidelines also recommend that caloric intake should be sufficient to achieve and maintain optimal growth and body weight.[318] In general, the overall recommendations of the ADA and ISPAD are consistent with recommendations in the *Dietary Guidelines for Americans,*[319] which emphasize incorporation of fruits, vegetables, whole grains, and low-fat food choices.

Type 1 Diabetes Mellitus

With the exception of 1 study,[320] the dietary intake of youth with T1DM failed to meet nutritional recommendations, with fruit, vegetable, and whole grain intake below and fat intake above recommended quantities.[321–326] Adherence to the Dietary Approaches to Stop Hypertension (DASH) diet, which prescribes a high proportion of fruits and vegetables, was associated with lower BP, better ratio of LDL to HDL, and lower HbA_{1c} in youth with T1DM.[327,328] Sugar-sweetened beverage consumption and diet beverage consumption have been associated with adverse lipid, BP, and HbA_{1c} levels, which may be a marker for other concurrent unhealthy lifestyle behaviors (eg, unhealthy diet, sedentary lifestyle, and increased screen time).[329] Dietary knowledge, adherence, and family involvement may play a role in diet quality and improved glucose. Monitoring of carbohydrate intake through carbohydrate counting is an important strategy to improve glucose control.[330] However, reduction of carbohydrate may contribute to increased fat intake as diabetes mellitus management (to improve glucose control) and may have negative effects on cardiovascular health.[331,332] Youth with T1DM have documented higher fat intakes that are positively associated with HbA_{1c} levels.[333]

Disturbed eating behaviors are common among youth with T1DM. These behaviors tend to cluster around increased dietary restraint (conscious restriction of food intake), binge eating,[334] and poor diet quality.[335,336] Many adolescents report weight and body shape concerns, unhealthy weight control behaviors, diminished self-worth, and depression.[337–339] Disturbed eating behaviors are more prevalent with increased BMI[335,336] and with the perception of being overweight.[340] Disturbed eating behaviors, coupled with unhealthy weight control behaviors, have been associated with adverse glucose control.[338,341] Up to 50.4% of male and female adolescents with T1DM reported using weight control behaviors.[338] Insulin omission and insulin underdosing are the most serious weight control behaviors reported. In an 11-year longitudinal study of adult women, insulin restriction was found to be significantly associated with increased morbidity and mortality with a 3.2-times increased risk of death after controlling for age, BMI, and HbA_{1c}.[342]

Type 2 Diabetes Mellitus

Youth with T2DM also fail to meet nutritional recommendations. The baseline dietary assessments from the TODAY study revealed that only 1% of youth met the ADA recommendation

for <7% intake of saturated fat.[343] Adherence to the DASH diet was associated with improved LDL particle density and BMI in youth with T2DM.[327] No studies examining micronutrient intake in youth with T2DM were found.

One study examined dietary adherence among youth with T2DM using a telephone survey of patients from 1 diabetes mellitus clinic. The participants reported that the greatest difficulty in diabetes mellitus self-management was adhering to dietary recommendations. Most subjects reported overeating at least once weekly, drinking sugar-sweetened beverages at least once daily, and eating fast food >4 times per month.[344] Consistent with studies in T1DM youth, disturbed eating behaviors were common and associated with being overweight in both male and female subjects and with poor glucose control in female subjects.[340] In a telephone survey, dietary recommendations were reported to be challenging to achieve, and the participants reported that they frequently overate, drank sugar-sweetened beverages, and ate fast food. The greatest reported challenges to healthy eating were feeling stressed or sad, having food cravings, and eating outside of the home.[344]

In summary, adherence to carbohydrate counting and the DASH diet has been associated with improved CVD markers. High fat intake is a consistent dietary pattern that requires additional strategies to minimize. Youth with T1DM and T2DM who exhibit disturbed eating behaviors or body weight dissatisfaction, are overweight, or perceive themselves to be overweight are at risk for participation in unhealthy weight control behaviors and poor glucose control, which can lead to vascular complications.

Exercise

Youth with T1DM and T2DM appear to be more sedentary and less fit than nondiabetic youth.[344a–351] PA is not associated with glycemic outcomes in some large studies[352,353] but was among the factors most strongly associated with HbA_{1c} in the Diabetes Patientien Verlaufsdokumentation (DPV) study.[354] In contrast, physical fitness among youth with T1DM and T2DM is more consistently associated with lower HbA_{1c}.[346,355–357] Small studies have reported that aerobic and strength training yields increased fitness and decreased daily insulin dosage compared with normal daily activities[358] and that greater PA improves fitness without changing HbA_{1c}.[359] In a large study of overweight/obese and sedentary children, 3 months of aerobic training yielded dose-dependent improvements in IR and adiposity compared with usual PA.[360]

Psychosocial Stress

Stressful life events among adolescents with diabetes mellitus are associated with negative emotional reactions and worse diabetes mellitus control, in part as a result of poor self-care.[361] Good family relations may lower HbA_{1c} among girls.[361] Surprisingly, diabetes mellitus and its management were not a common theme among stressors reported by youth with T1DM.[362] Family stress may be associated with higher HbA_{1c},[363] perhaps mediated by anxiety in the child.[364] Adolescents who perceive their parents as more controlling report greater depressive symptoms, whereas those who perceive their parents as accepting have lesser depressive symptoms.[365] General stress among parents is associated with more depressive symptoms and poorer self-care, glucose control, and blood glucose monitoring,[366] whereas diabetes mellitus–specific stress among parents is associated with more frequent blood glucose monitoring and better child-reported self-care.[366]

Depression

Depression among youth with diabetes mellitus has been associated with poorer diabetes mellitus control, increased complications, and greater service use.[367] A meta-analysis of 22 case-control studies found that psychological problems, including depressive symptoms, were more likely among children with versus without diabetes mellitus,[368] although exceptions exist.[369,370] In a large study of youth with T1DM, 17% had significant depressive symptoms, half of whom did not discuss these symptoms with their pediatrician or nurse.[371] Some depressive symptoms overlap with diabetes mellitus–related physical symptoms; however, youth with diabetes mellitus endorse all depressive symptoms more frequently than youth without diabetes mellitus.[372]

Depressive symptoms may be associated with poorer blood glucose monitoring[373,374] and poorer diabetes mellitus control.[361,375–377] Depressive symptoms are also associated with impaired hypoglycemia awareness[378] and may independently predict proteinuria.[379] A study of 276 adolescents with diabetes mellitus found that blood glucose monitoring frequency explains 38% of the association between HbA_{1c} and depressive symptoms (ie, with depressive symptoms, blood glucose monitoring decreases and HbA_{1c} increases).[380] A large study of adolescents at risk for T2DM by virtue of high BMI together with a family history of diabetes mellitus found that depressive symptom severity was directly associated with BMI and fasting insulin levels.[381] However, other studies have not found associations between emotional/behavioral problems and metabolic control.[382] Screening for depression is advised for adolescents overall,[383] and this may be especially important for those with diabetes mellitus.

Sleep

Alterations in sleep (time, disruption, architecture, and quality) are associated with neuroendocrine changes in appetite,[384] sympathetic nervous system arousal,[385] and metabolic dysregulation.[385,386] In the general adult population and in healthy children and adolescents, sleep alterations may adversely influence glucose regulation,[385] C-reactive protein,[387] and lipids[388] and increase the risk for hypertension, T2DM, heart attack, and stroke.[389,390] Reports of reduced sleep times of up to 64%[391] have been documented for children and adolescents with diabetes mellitus who confront additional challenges with sleep as a result of diabetes mellitus management[392,393] that may further disrupt sleep and add to adverse cardiovascular outcomes.

In adults with T1DM, short sleep duration was associated with reduced insulin sensitivity,[394] increased HbA_{1c},[395] and a greater prevalence of nondipping BP patterns.[395,396] Additionally, 2 polysomnographic studies revealed that those with T1DM spent more sleep time in lighter stages of sleep (stages 1 and 2) and less time in restorative slow-wave sleep (stage 3) compared with healthy control subjects.[397,398] One observational study compared sleep stages in youth with T1DM and age-, sex-, and BMI-matched control subjects.[399] Consistent with adult studies, the diabetic cohort spent

significantly more time in stage 2 and less time in stage 3 sleep than the control group. Within the diabetic cohort, those who spent the most time in stage 2 sleep also had higher daily glucose and HbA_{1c} levels, suggesting metabolic dysregulation with lighter sleep.[399] The association of hypoglycemia with depth of sleep has been conflicting[400,401]; however, fluctuations in glucose levels (≥25 $mg \cdot dL^{-1} \cdot h^{-1}$), even when the blood glucose level remained within normal ranges, have been associated with sleep disruption.[400] Because glycemic variability is associated with cardiovascular risk, the potential impact of nocturnal glucose variability on cardiovascular health requires further research. Obstructive sleep apnea, associated with obesity in children, may augment CVD risk in those affected.[402]

Nonmodifiable Risk Factors

Genetics and Family History

Nonmodifiable CVD risk factors for both T1DM and T2DM include genetics, family history, and diabetes mellitus duration. There have been numerous investigations into genetic risk factors for CVD in general[403] and in T1DM specifically.[404,405] Systems under investigation for potential increased genetic risk for CVD in T1DM were reviewed by Orchard et al[20] and include polymorphisms in the receptors for advanced glycation end products, angiotensin-converting enzyme, neuropeptide Y, hepatic lipase, apolipoprotein A-IV, von Willebrand factor, haptoglobin, nitric oxide synthase, and adiponectin, among others.[20,406] Similarly, genetic variation in *CALPN10*, *FABP4*, *GK*, *GST*, *PPARA*, and *PPARG* may be associated with increased CVD risk in people with T2DM, but the evidence is inconclusive.[407]

Family history of premature CVD is an established and independent risk factor for the development of CVD.[408,409] For example, the AHA scientific statement on cardiovascular risk reduction in high-risk pediatric populations[4] identifies a family history of premature coronary artery disease in expanded first-degree pedigrees (corresponding to male family members <55 years of age and female family members <65 years of age) as a risk factor for CVD in patients with T1DM and T2DM. The ADA[3] and American Academy of Pediatrics[57] recommendations are similar. Collectively, the major professional organizations agree that family history of early CVD is a major risk factor for the development of early CVD in patients with both T1DM and T2DM. In patients with T1DM, family history of T2DM increased CVD[410] and in the DCCT/EDIC was associated with increased weight gain and a more atherogenic CVD profile among those in the intensive intervention arm in the highest quartile of weight gain.[411]

Gaps in Knowledge

Data from the observational studies add to our understanding of the pathophysiology and current clinical practices and highlight needs for improved care. Better methods of glucose control and management of other CVD risk factors are required for both T1DM and T2DM. The data from randomized, clinical trials such as the TODAY study in youth with T2D[60] and those anticipated from the Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial (AdDIT) study in youth with T1DM will begin to provide much-needed data on the management of CVD risk factors in diabetes mellitus.[412] Participants in TODAY were treated for hypertension and dyslipidemia per study protocols, and although these were not the primary study aims, these longitudinal data will inform the management of these CVD risk factors in youth with T2DM. Similarly, the AdDIT study should soon provide data on the use of statins and angiotensin-converting enzyme inhibitors in adolescents with T1DM. Uncertainty remains for both the safety and efficacy of cardiovascular risk factor treatment in youth with diabetes mellitus (Table 3).

Given the current funding environment, it is unlikely that many of these research questions will be addressed in long-term, randomized, clinical trials. Pediatric providers will continue to need to combine various sources of evidence and to generate inferences from data in adults to determine the best possible treatment decisions for youth with diabetes mellitus and their families.

Summary/Priorities to Improve Cardiovascular Health

The most recent AHA/ADA position statement on the primary prevention of CVD in diabetes mellitus found that the current state of knowledge[413] did not allow the differentiation of guidelines for T1DM and T2DM. Moreover, the differentiation of T1DM and T2DM in youth can be challenging and is beyond the scope of this article.[414] However, >80% to 90% of youth diagnosed with T1DM will have evidence of autoimmunity, and T2DM is exceedingly rare in prepubescent children or in children with BMI <85th percentile for age and sex.[415] It remains an unanswered question as to whether pathophysiological differences exist in CVD risk in youth with T1DM and T2DM and, if so, whether preventive measures and therapeutics could be targeted more effectively. For example, pathophysiological differences could be presumed between two 15-year-olds, one with a recent diagnosis of autoimmune T1DM who is lean and the other with a BMI >99th percentile and T2DM. In contrast, IR is a well-established component of both T2DM and T1DM,[84,250]

Table 3. Gaps in Knowledge: Research Questions

What is the role for clinical trials of lifestyle interventions such as dietary and exercise modifications to improve CVD health?
What is the appropriate age to begin CVD risk factor screening?
What goals should be used for CVD risk factors?
At what age should pharmacological therapy be considered?
Should treatment goals for CVD risk factors be the same as those for adults or less or more stringent?
What are the risks of potential lifetime pharmacological treatment for CVD risk factors (or conversely of delaying such treatment until adulthood)?
What is the magnitude of teratogenic risk from pharmacological treatment of CVD risk factors in adolescent female patients?
What is the cost-benefit ratio of pharmacological treatment for CVD risk factors?
How will advances in glucose management such as the artificial pancreas affect CVD risk in T1DM?
How will population changes in obesity affect CVD risk in both T1DM and T2DM?
Do pathophysiological differences exist in CVD for T1DM vs T2DM?

CVD indicates cardiovascular disease; T1DM, type 1 diabetes mellitus; and T2DM, type 2 diabetes mellitus.

and youth with T1DM are increasingly obese instead of historically being thin as a result of poor glucose control.[221] Moreover, the DCCT/EDIC study suggests that intensive management of T1DM may result in increased BMI and associated CVD risk factors, especially in people with T1DM who have a family history of T2DM.[224,411,416] One might speculate that advances such as the artificial pancreas will improve glucose control but may also result in increases in obesity and possibly IR, with the cardiovascular risk factor profile in T1DM becoming more similar to those with T2DM. Therefore, although alternative strategies to reducing CVD risk in youth with diabetes mellitus are required, intensive glucose control remains the foundation of diabetes mellitus management. Priorities to improve cardiovascular health in youth with diabetes mellitus are listed in Table 4.

Table 4. Priorities to Improve Cardiovascular Health in Youth With Diabetes Mellitus

Determination of appropriate screening guidelines for CVD risk factors
Recognition of cut points for initiation of treatment of CVD risk factors
Increasing rates of treatment of CVD risk factors
More information on associations of CVD risk factors with target organ damage (and the appropriate use of surrogate markers)
Better understanding of optimal treatment, including well-defined goals, and optimal levels for CVD risk factors
Improved methods to prevent development of early atherosclerosis
Safety and efficacy evaluations of pharmacological treatments targeting glucose control that offer additional pleiotropic CVD benefits

CVD indicates cardiovascular disease.

Conclusions

In this statement, we have reviewed recent guidelines[2–7] on CVD in youth with diabetes mellitus with an emphasis on new data that have emerged since their publication. Both T1DM and T2DM are increasing in youth, and current data indicate that elevated CVD risk factors are common but rarely treated pharmacologically. Clinical trial data are needed to inform the question of the appropriateness of pharmacological treatment of CVD risk factors. Prevention of future CVD in youth with diabetes mellitus will require advances in research and their translation to clinical care to prevent the development of CVD risk factors and to determine their optimal treatment when they do exist.

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*Modest.

†Significant.

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Cardiovascular Disease Risk Factors in Youth With Diabetes Mellitus: A Scientific Statement From the American Heart Association

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Supplement 1; Brief Descriptions of On-Going Large Multi-Center Observational and Interventional Research Studies

Studies in Progress: Observational

SEARCH for Diabetes in Youth is an ongoing, multicenter, observational study designed to estimate the population prevalence and incidence of diabetes by type, age, gender, and ethnicity in individuals under age 20 years as well as to describe the clinical characteristics, clinical course, and complications of diabetes and develop practical approaches to diabetes classification[56]. Active surveillance for all cases of physician-diagnosed diabetes, excluding gestational diabetes, is conducted in geographically defined populations located at four sites (Cincinnati, Colorado, Seattle, and South Carolina) and in membership based health plans at two sites (Hawaii and Southern California) using networks of endocrinologists, other health care providers, hospitals, existing pediatric diabetes databases, health plan databases, and administrative databases as well as death certificate searches. Data are collected at the time of enrollment and annually thereafter and include patient interviews, physical examinations, anthropometry, BP, medical records reviews, and documentation of risk factors for complications and processes of care as well as several laboratory studies for diabetes autoantibodies, C-peptide, HbA1c, blood glucose, lipids, and urine albumin and creatinine. The study was initiated in 2000 and is expected to continue until 2015.

Diabetes Patientien Verlaufsdokumentation (DPV)

Initiated in 1990, the German/Austrian Diabetes Patientien Verlaufsdokumentation (DPV) is a prospective, standardized, multicenter, electronic data acquisition system designed to collect data on the clinical care and health outcomes of adults and children with diabetes[57]. Over 300 participating health care facilities, including hospitals, clinics, diabetes specialized practices, and general practitioner or primary care offices from Germany and Austria presently contribute data, which is used for patient care, quality assurance/benchmarking and epidemiologic and clinical research. De-identified demographic and clinical data that were recorded locally as part of routine outpatient and inpatient care are submitted to a central center for data integrity checking and statistical analyses every 6 months.

Type 1 Diabetes Exchange

The T1D Exchange Clinic Network is a registry of adults and children with T1D and is one of three parts of the T1D Exchange, which was initiated in 2010, in addition to a patient centered on line community (called Glu http://www.t1dexchange.org/core-values-and-mission-statement/glu/) and a biobank to store biological samples for use by researchers[58]. Over 26,000 people with T1D from 70 centers in the U.S. have been enrolled with goals of: 1) identifying and addressing pertinent clinical issues; 2) conducting exploratory/hypothesis generating analyses; and 3) categorizing participants for future clinical studies[58].

Interventional:

The Adolescent type I Diabetes cardio-renal Intervention Trial (AdDIT) is a multi-center, randomized, double-blind, placebo-controlled trial designed to evaluate whether treatment with an angiotensin converting enzyme inhibitor (ACEI) or a statin, alone or in combination, in high risk adolescents with T1D can improve early surrogate markers of diabetic nephropathy and CVD[59]. Clinical centers located in the United Kingdom, Australia, and Canada will recruit 500 adolescents, ages 11-16 years with T1D diagnosed for more than one year who are at high risk for diabetic nephropathy and CVD. Patients will be randomized to receive either Quinapril (ACEI) at 10g daily or Atorvastatin (Statin) at 10 mg daily or combination therapy or placebo in a 2 X 2 factorial design for 3-4 years. The primary aim of the trial is to demonstrate a significant reduction in albumin excretion and the incidence of microalbuminuria. Secondary objectives of the trial will be to determine the effects of treatment on surrogate CV outcomes including endothelial dysfunction, subclinical atherosclerosis, and arterial stiffness, CVD risk factor levels, and CVD risk markers as well as renal function. The trial is scheduled to be completed fall 2013. It will be the first major trial to provide data on the most effective strategy of

managing high risk adolescents with T1D in order to reduce risk for future morbidity and mortality from diabetic nephropathy and CVD.

Treatment Options for Type 2 Diabetes in Adolescents and Youth: TODAY Study

TODAY was a multicenter, randomized-controlled trial studying treatment options in youth with T2D. Participants were recruited from 15 study centers across the US between 2004 and 2009 and followed for a minimum of two years and a maximum of 6 years mean follow-up time was 3.86 years[44, 60]. Eligibility criteria included children from 10 to 17 years of age, diagnosed with T2D within the last 2 years, with negative pancreatic auto-antibodies, sustained c-peptide and a BMI greater than the 85th percentile for age and sex[61]. Of the 1,206 obese subjects screened and considered clinically to have T2D, 118 (9.8%) were positive for GAD-65 and/or insulinoma-associated protein 2 (IA-2) autoantibodies antibodies; of these, 71 (5.9%) were positive for a single antibody, and 47 were positive (3.9%) for both antibodies[61, 62]. Thus, without islet autoantibody analysis, it is difficult to reliably distinguish between T1D and T2D in obese youth.

699 subjects were randomized 1:1:1 between each of three arms: metformin alone, metformin plus rosiglitazone, or metformin plus intensive lifestyle intervention[44]. In the lifestyle arm, participants met with a physical activity and nutrition leader weekly for six months then biweekly for six months, and then quarterly for the remainder of the study, using a lifestyle intervention program designed by the TODAY study specifically for use in low-income and minority youth[63]. The primary endpoint for the study was treatment failure, defined as a HbA1c >8% for 6 months, or sustained metabolic decompensation requiring insulin therapy[60].

The results of TODAY indicate that monotherapy with metformin does not provide sustained control of glycemia in many youth with T2D and suggest that combination therapy will be required. While rosiglitazone appeared most effective in the adolescents in TODAY, in adults, the use of agents in the thiazolidinedione class has now declined due to cardiovascular and bone density safety concerns[64, 65]. However, serious adverse events did not differ between arms in TODAY. Longer-term follow-up of TODAY participants (TODAY2) will provide further insights into complications of youth-onset T2D. In addition, TODAY data argue that early interventions aimed at sustaining beta cell function may be the most beneficial approach to management of T2D.