Cardiovascular Risk Factors Among Youth With and Without Type 2 Diabetes

Differences and possible mechanisms

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OBJECTIVE — To compare cardiovascular disease (CVD) risk factors among recently diagnosed youth with type 2 diabetes and nondiabetic youth and investigate whether demographic, behavioral, or metabolic factors might account for observed differences.

RESEARCH DESIGN AND METHODS — Data from 106 type 2 diabetic and 189 nondiabetic multiethnic youth, aged 10–22 years, were analyzed. Prevalence of CVD risk factors were age and race/ethnicity adjusted using direct standardization. Multiple linear regression models were sequentially adjusted for demographic, behavioral (dietary saturated fat intake and physical activity), and metabolic (body adiposity and glycemia) factors to explore possible mechanisms associated with differences in CVD risk factors between the case and control groups.

RESULTS — Compared with control subjects, youth with type 2 diabetes had a higher prevalence of elevated blood pressure, obesity, large waist circumference, low HDL cholesterol, high triglycerides, and high albumin-to-creatinine ratio ($P < 0.05$ for each risk factor). Type 2 diabetic youth also had higher levels of apolipoprotein B, fibrinogen, interleukin (IL)-6, C-reactive protein, and leptin; lower adiponectin levels; and denser LDL particles ($P < 0.05$ for each risk factor). Adjustment for BMI, waist circumference, and A1C substantially attenuated differences in the CVD risk factors between the case/control groups, except for fibrinogen and IL-6, which remained significantly higher in type 2 diabetic youth.

CONCLUSIONS — Compared with control youth, type 2 diabetic youth have a less favorable CVD risk factor profile. Adiposity and glycemia are important contributors to differences in CVD risk profiles among type 2 diabetic and control youth. Inflammatory and prothrombotic factors may also play an important role.

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There has been a dramatic increase in the prevalence of type 2 diabetes in children and adolescents during the past two decades (1). Much of the health burden of type 2 diabetes in youth will result from chronic complications, including cardiovascular disease (CVD) (2).

In adults with type 2 diabetes, CVD occurs earlier and is associated with higher mortality compared with the general population (3). Early adult-onset type 2 diabetes (diagnosed age 18–44 years) has been associated with more aggressive CVD than later-onset type 2 diabetes (4),

suggesting that CVD complications resulting from type 2 diabetes diagnosed in youth may be even more unfavorable.

Obesity, dyslipidemia, hypertension, and smoking have long been recognized as major risk factors for cardiovascular morbidity and mortality in adults. The typical lipid abnormalities in type 2 diabetic adults are low levels of HDL cholesterol and high levels of triglycerides (5). Studies have recently identified novel lipid abnormalities, including a preponderance of small, dense LDL particles and high levels of apolipoprotein B (apoB) (6). Other novel CVD risk factors indicate systemic inflammation, a prothrombotic state, and endothelial dysfunction, marked by altered levels of interleukin (IL)-6, C-reactive protein (CRP), fibrinogen, adipocytokines, and microalbuminuria.

Given the recent emergence of type 2 diabetes in adolescent populations, the relationship between type 2 diabetes and CVD risk factors among youth has not been well characterized. Although type 2 diabetes itself is considered a risk factor for CVD, we hypothesized that youth with recently diagnosed type 2 diabetes would have a less favorable CVD risk factor profile, excluding diabetes status, compared with nondiabetic youth. We also explored whether measures of adiposity (BMI and waist circumference), hyperglycemia, and behavioral factors (physical activity and dietary intake of saturated fat) may account for observed differences in CVD risk factors between type 2 diabetic and nondiabetic youth.

RESEARCH DESIGN AND METHODS
— The study population included participants in the SEARCH Case-Control (SEARCH-CC) study, an ancillary study to the multicenter SEARCH for Diabetes in Youth study (7). SEARCH study participants who were residents of Colorado or South Carolina, aged 10–22 years, and African American, Hispanic, or non-Hispanic whites were invited to participate in the SEARCH-CC study. Because of recruitment from the larger SEARCH study, which had ascertained case subjects diagnosed through

age 19 years, the oldest of the case subjects had aged to 22 years at the time of recruitment into the SEARCH-CC study. Case subjects were identified using networks of health care providers. Type 2 diabetes was defined by provider diagnosis. In our population, provider classification of diabetes type was previously found to be consistent with the expected clinical and biochemical characteristics, including low frequency of insulin treatment, absence of autoimmune markers, and presence of markers of insulin resistance among youth with type 2 diabetes (8). Overall, 52% of the eligible SEARCH study youth with type 2 diabetes participated in the SEARCH-CC study. Nondiabetic control youth, aged 10–22 years and self-identified as African American, Hispanic, or non-Hispanic white, were recruited from primary care offices in the same geographic areas. Nondiabetic status in the control subjects was confirmed by fasting glucose values. Primary care practices were chosen as the sampling frame for control subjects in order to closely represent the underlying population that gave rise to the type 2 diabetic case subjects. Additional details regarding sampling and recruitment for the SEARCH-CC study have been published (9). Written informed consent was obtained from participants aged ≥18 years, and assent was obtained for participants aged <18 years.

Outcome measures
Blood was drawn after an overnight fast for measurement of total cholesterol, triglycerides, HDL cholesterol, apoB, lipoprotein cholesterol distribution, and calculation of the LDL relative flotation rate (R_f), fibrinogen, IL-6, CRP, leptin, and adiponectin. A morning spot-urine sample was collected for measurement of urinary albumin and creatinine for calculation of the albumin-to-creatinine ratio (ACR) (micrograms of albumin per milligram of creatinine). Specimens were processed and shipped within 24 h to the Northwest Lipid Metabolism and Diabetes Research Laboratories for analyses. Measurements of plasma cholesterol, triglycerides, and HDL cholesterol were performed enzymatically on a Hitachi 917 autoanalyzer. LDL cholesterol was calculated by the Friedewald equation for triglyceride concentrations <400 mg/dl (4.52 mmol/l/l) and by the BetaQuantification procedure for triglycerides ≥400 mg/dl (10). ApoB was measured by a calibrated nephelometric system. The li-

poprotein cholesterol distribution used a modification of a previously described technique (11). Urinary albumin was measured by nephelometry, and urinary creatinine was measured by the Jaffe method using a Roche Diagnostics reagent on the Hitachi 917 autoanalyzer. Serum IL-6 concentrations were determined by a capture sandwich immunoassay using a Bio-Plex suspension array system and commercially available reagents from Linco Research. High-sensitivity CRP and fibrinogen were assayed by a Dade Behring nepholometer using Behring reagents.

Three sitting blood pressure measurements were obtained and averaged. Current smoking status was obtained from self-report. Height was measured to the nearest 0.1 cm by stadiometer. Weight was measured to the nearest 0.1 kg using an electronic scale. Waist circumference was measured to the nearest 0.1 cm using the National Health and Nutrition Examination Survey protocol (12). Anthropometric measurements were taken twice and averaged. Height and weight measurements were used to calculate BMI (kg/m^2).

Categorical CVD risk factors were defined as elevated blood pressure (systolic or diastolic blood pressure ≥95th percentile for age, sex, and height or use of antihypertension medication), obesity (BMI ≥95th percentile for age and sex), large waist circumference (≥90th percentile for age and sex), high LDL cholesterol (≥130 mg/dl), low HDL cholesterol

(≤35 mg/dl), high triglycerides (≥150 mg/dl), current smoking, and elevated urinary ACR (≥30 μg/mg) (13,14).

Covariates
Race/ethnicity was obtained from self-report using 2000 Census–based questions (15). Fasting A1C was measured by an ion exchange high-performance liquid chromatography instrument. Dietary intake was ascertained using a modified version of the Kids Food Questionnaire (16). Saturated fat intake was calculated as grams per 1,000 kcal. Physical activity was obtained by self-report using questions based on the Youth Risk Behavior Surveillance System (17) and was categorized as the average number of 30-min blocks of moderate-to-vigorous activity per day. Self-reported Tanner staging was used to categorize pubertal development using scales ranging from 1 (prepubertal) to 5 (adult).

Statistical analysis
Statistical analyses were performed using PC-SAS (version 9.1). Two sets of analyses were performed. In the first analysis, eight CVD risk factors were categorized to compare risk factor prevalence between type 2 diabetic and nondiabetic youth. The Breslow-Day test was used to evaluate interactions between race/ethnicity and age-group categories (10–15 vs. 16–22 years) and diabetes status. None of the interactions were significant (all *P* values >0.05); thus, all race/ethnicity and age-groups were included together in the

Table 1—Demographic, metabolic, and behavioral characteristics of the study participants

Characteristic	Type 2 diabetes	Control subjects	*P*
n	106	189	
Female [*n* (%)]	73 (69)	113 (60)	0.12
Race/ethnicity [*n* (%)]			
African American	58 (55)	54 (29)	
Hispanic	18 (17)	32 (17)	<0.0001
Non-Hispanic white	30 (28)	103 (54)	
Age (years)	15.7 (4.4)	14.3 (4.6)	0.0001
Age at diagnosis (years)	13.7 (4.0)	—	—
Duration of diabetes (years)	1.5 (1.4)	—	—
A1C (%)	7.4 (2.6)	5.2 (0.4)	<0.0001
BMI (kg/m^2)	35.0 (8.7)	23.7 (7.1)	<0.0001
Waist circumference (cm)			
Female	108.3 (22.1)	80.4 (16.4)	<0.0001
Male	110.2 (13.9)	77.2 (20.3)	<0.0001
Saturated fat [(g)/1,000 kcal]	14.8 (4.3)	13.9 (3.6)	0.005
Physical activity*	4.8 (6.3)	5.6 (6.3)	0.17

Data are means (interquartile range), unless otherwise noted. *Number of 30-min blocks of moderate-to-vigorous physical activity per day.

analyses. Prevalence estimates of CVD risk factors were age and race/ethnicity adjusted using direct standardization. Differences in adjusted prevalence between the case/control groups were evaluated using χ^2 tests.

In a second set of analyses, multiple linear regression models were used to explore differences in CVD risk factors (modeled as continuous variables) between case and control youth. All models were adjusted for demographic factors (age, sex, and race/ethnicity) and then sequentially adjusted for behavioral factors (dietary saturated fat intake and physical activity), adiposity (BMI and waist circumference), and glycemic control (A1C). A final, fully adjusted model included all covariates significantly associated with any CVD risk factor. Comparison of these models allowed investigation of possible mechanisms that may account for differences in specific CVD risk factors between type 2 diabetic and control youth. Nonnormally distributed variables (triglycerides, apoB, IL-6, and CRP) were log transformed for statistical testing, and differences in geometric means are reported to present these variables in their original scale. Estimated differences were positive when values for diabetic youth were greater than for control youth. In separate models for each CVD risk factor, waist circumference only or BMI only were entered into the models instead of both measures to investigate if the distribution of body fat, rather than overall adiposity, might differentially account for discrepant levels among diabetic and control youth.

RESULTS — The analyses included data from type 2 diabetic ($n = 106$) and nondiabetic ($n = 189$) youth, with data on CVD risk factors and covariates. Only diabetic case ($n = 95$) and control ($n = 174$) subjects with complete data on all eight categorized CVD risk factors were used in the analysis comparing CVD risk factor prevalence between the case and control groups. Demographic, metabolic, and behavioral characteristics of the diabetic and control participants are shown in Table 1. Compared with control youth, diabetic youth were slightly older, more likely to be African American, had higher mean BMI and A1C, and had a greater intake of saturated fat per 1,000 kcal. Table 2 shows that youth with diabetes had higher age- and race/ethnicity-adjusted prevalence of elevated blood pressure, obesity, large waist circumference, low

HDL cholesterol, high triglycerides, and high ACR. There was little difference between diabetic and control youth in the adjusted prevalence of high LDL cholesterol or current smoking.

Figure 1 shows that of eight categorical CVD risk factors the overall distribution of the total number of CVD risk factors (0, 1, 2, 3, or >4) in youth was significantly different ($P < 0.0001$), with a less favorable CVD risk profile for diabetic youth. A total of 60.0% of diabetic youth had three or more CVD risk factors, compared with 13.1% of nondiabetic control youth. Diabetic youth had an average of 2.9 risk factors compared with 1.0 among control youth ($P < 0.0001$).

Table 3 shows the adjusted means and mean differences for each CVD risk factor for diabetic and nondiabetic youth. In model 1, adjusted only for demographic variables, diabetic youth had higher levels of triglycerides, systolic blood pressure, apoB, fibrinogen, IL-6, CRP, and leptin; lower levels of HDL cholesterol and adiponectin; and greater LDL particle density compared with nondia-

betic youth. There were no significant differences in mean LDL cholesterol between the groups (data not shown). Adjustment for BMI and waist circumference (model 2) substantially attenuated the differences in HDL cholesterol, systolic blood pressure, CRP, and adiponectin between the two groups. This adjustment for adiposity reversed the direction of the difference in leptin levels between the groups such that control youth had a 38% higher average leptin level than diabetic youth. In model 3, adjustment for A1C significantly attenuated the differences between case and control subjects in apoB, LDL R_f, and CRP levels. There was also a substantial lessening of the differences in triglyceride levels (a 58% reduction) with adjustment for A1C. Adjustment for behavioral factors did not significantly influence the mean differences between diabetic and nondiabetic youth for any of the CVD risk factors (data not shown). In model 4, adjustment for all of the demographic and metabolic factors (age, sex, race/ethnicity, BMI, waist circumference, and A1C) resulted in a

Table 2—*Prevalence of CVD risk factors in type 2 diabetic and nondiabetic youth, adjusted for age and race/ethnicity*

	Prevalence*		
CVD risk factor	Type 2 diabetic subjects ($n = 95$)	Control subjects ($n = 174$)	P
Elevated blood pressure	27 (18–36)	5 (2–8)	<0.0001
Obesity	86 (79–93)	26 (19–33)	<0.0001
Large waist circumference	82 (74–90)	22 (16–28)	<0.0001
Low HDL cholesterol	25 (16–34)	5 (2–8)	<0.0001
High triglycerides	27 (18–36)	6 (2–10)	<0.0001
High ACR	17 (9–25)	7 (3–11)	0.02
High LDL cholesterol	14 (7–21)	10 (6–14)	0.29
Current smoking	5 (1–9)	7 (3–11)	0.56

Data are % (95% CI). *Only participants with complete data on these eight CVD risk factors were used in this analysis.
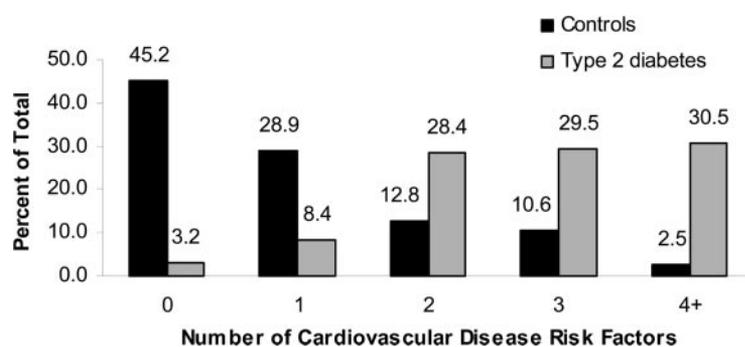

Figure 1—*Distribution of eight CVD risk factors in youth with and without type 2 diabetes. *P < 0.0001. Risk factors include elevated blood pressure, obesity, large waist circumference, low HDL cholesterol, high triglycerides, high LDL cholesterol, high ACR, and current smoking.*

Table 3—*Means and mean differences of CVD risk factors for type 2 diabetic and nondiabetic control youth, adjusted for demographic and metabolic characteristics*

CVD risk factor	Type 2 diabetic subjects	Control subjects	Mean difference*	*P*
HDL cholesterol (mg/dl)				
Model 1	42 (39–45)	50 (47–53)	−8	<0.0001
Model 2	47 (44–50)	48 (45–50)	−1	0.5
Model 3	42 (38–45)	50 (47–53)	−8	<0.0001
Model 4	46 (43–50)	48 (46–51)	−2	0.4
Triglycerides (mg/dl)†				
Model 1	114 (98–133)	74 (65–84)	40	<0.0001
Model 2	102 (86–122)	78 (68–89)	24	0.01
Model 3	95 (80–112)	78 (68–88)	17	0.04
Model 4	86 (71–104)	81 (71–92)	5	0.6
Systolic blood pressure (mmHg)				
Model 1	115 (111–118)	107 (104–110)	8	<0.0001
Model 2	110 (106–113)	109 (106–112)	1	0.7
Model 3	114 (110–117)	107 (104–110)	7	0.002
Model 4	109 (105–113)	109 (106–112)	0	0.9
ApoB (mg/dl)†				
Model 1	83 (76–92)	60 (55–65)	23	<0.0001
Model 2	76 (68–85)	61 (57–66)	15	0.001
Model 3	69 (62–77)	63 (58–68)	6	0.1
Model 4	65 (57–73)	64 (60–69)	1	0.9
LDL particle density (R_f)				
Model 1	0.262 (0.255–0.268)	0.284 (0.278–0.262)	−0.022	<0.0001
Model 2	0.266 (0.259–0.274)	0.282 (0.276–0.288)	−0.016	0.001
Model 3	0.274 (0.266–0.281)	0.280 (0.275–0.286)	−0.007	0.1
Model 4	0.277 (0.269–0.285)	0.279 (0.274–0.285)	−0.002	0.6
Fibrinogen (mg/dl)				
Model 1	442 (420–465)	310 (292–328)	132	<0.0001
Model 2	410 (387–433)	319 (303–336)	91	<0.0001
Model 3	428 (400–455)	314 (295–332)	114	<0.0001
Model 4	395 (369–422)	323 (306–340)	72	<0.0001
IL-6 (pg/dl)†				
Model 1	7.9 (5.2–11.1)	2.9 (2.0–4.0)	5.0	<0.0001
Model 2	6.8 (4.2–11.0)	3.0 (2.1–4.2)	3.8	0.005
Model 3	7.3 (4.3–12.3)	2.9 (2.1–4.1)	4.4	0.004
Model 4	6.5 (3.7–11.4)	3.0 (2.1–4.3)	3.5	0.03
CRP (mg/dl)†				
Model 1	0.20 (0.12–0.33)	0.07 (0.04–0.10)	0.13	0.0004
Model 2	0.07 (0.04–0.12)	0.09 (0.06–0.13)	−0.02	0.5
Model 3	0.12 (0.06–0.22)	0.08 (0.05–0.12)	0.04	0.2
Model 4	0.05 (0.03–0.08)	0.10 (0.07–0.14)	−0.05	0.03
Leptin (ng/dl)				
Model 1	24 (20–29)	15 (11–18)	9	0.0004
Model 2	13 (9–17)	18 (15–20)	−5	0.03
Model 3	26 (20–32)	14 (10–18)	12	0.0009
Model 4	15 (10–19)	17 (15–20)	−2	0.3
Adiponectin (μg/dl)				
Model 1	10.7 (9.0–12.3)	14.0 (12.6–15.3)	−3.3	0.0008
Model 2	12.4 (10.6–14.3)	13.5 (12.1–14.8)	−1.0	0.3
Model 3	10.8 (8.7–12.9)	13.9 (12.5–15.3)	−3.1	0.01
Model 4	12.4 (10.3–14.6)	13.5 (12.1–14.8)	−1.0	0.4

Data are means (95% CI). Model 1: adjusted for age, sex, and race/ethnicity. Model 2: model 1 plus BMI plus waist circumference. Model 3: model 1 plus A1C. Model 4: model 1 plus BMI, waist circumference, and A1C. *Estimated differences are positive when values for diabetic youth are more than control youth. †Geometric means are reported.

nearly complete attenuation of differences between case and control youth in most of the CVD risk factors, with the notable exceptions of higher fibrinogen and IL-6 levels in diabetic youth and higher CRP levels in nondiabetic youth. In the fully adjusted models, the levels of fibrinogen and IL-6 were 22 and 116% higher, respectively, and CRP levels were

50% lower for diabetic youth compared with control subjects.

Models evaluating waist circumference and BMI separately revealed similar results to models including both waist circumference and BMI, with the exception that waist circumference alone did not significantly attenuate the differences in leptin levels between the case/control subjects (data not shown). Including Tanner stage in the regression models in addition to age had minimal effect on the case/control subject difference in any CVD risk factor levels.

CONCLUSIONS — We found that youth with type 2 diabetes and a relatively short diabetes duration (average 1.5 years) have a higher prevalence of many CVD risk factors, including obesity and central fat deposition, elevated blood pressure, dyslipidemia, and elevated ACR, compared with nondiabetic youth of similar age, sex, and race/ethnicity. Moreover, youth with diabetes tend to have a cluster of multiple CVD risk factors, on average 2.9 vs. 1.0 in the control group. Data from the Bogalusa Heart Study (18) showed that the risk of fibrous plaques in the coronary arteries in youth with three or four CVD risk factors was three to eight times higher than the risk with zero, one, or two risk factors.

Our data show that youth with type 2 diabetes have an atherogenic dyslipidemia characteristic of adults with type 2 diabetes, including low HDL cholesterol, high triglycerides, and apoB and increased levels of LDL particle density. There were no significant differences in LDL cholesterol between case and control youth in our study. Elevated levels of apoB in the presence of normal LDL cholesterol levels have been associated with acute myocardial infarction in adults (19). Elevated apoB levels in the presence of normal LDL cholesterol levels may be explained by the increased concentration of triglyceride-rich apoB-containing lipoproteins and by the presence of dense LDL that is enriched in apoB relative to its cholesterol content. The association between type 2 diabetes and hypertension is well established in adults, and our findings support a similar relationship in youth.

Our findings suggest that adiposity and glycemic control account for much of the association between type 2 diabetes and an unfavorable CVD risk factor profile in youth. Excess adiposity, particularly visceral abdominal obesity, is a well-known risk factor for a cluster of metabolic abnormalities, including insulin resistance, dyslipidemia, and hypertension, and is in turn associated with the development of CVD. Consistent with data in adults (20), we found that adiposity, as measured by BMI and waist circumference, has a strong effect on differences in HDL cholesterol, triglycerides, and blood pressure levels between diabetic and nondiabetic youth.

Accumulating evidence indicates that adipose tissue releases a number of bioactive mediators that play an important role in the regulation of metabolic, inflammatory, and thrombolytic pathways that are associated with CVD risk (21). Most of these factors, including leptin, fibrinogen, IL-6, and CRP, are overproduced with obesity. Conversely, plasma levels of adiponectin, an insulin-sensitizing cytokine, are downregulated during obesity. We observed significantly higher levels of CRP, IL-6, fibrinogen, and leptin and lower levels of adiponectin in diabetic youth than in healthy control subjects. Consistent with a key role of obesity in the dysregulation of these adipocytokines and inflammatory factors in youth with type 2 diabetes, case-control differences disappeared (for adiponectin and leptin) or were even reversed (for CRP) on adjustment for adiposity. Nevertheless, fibrinogen and IL-6 remained significantly elevated in diabetic youth relative to nondiabetic youth, independent of demographic factors, adiposity, and glycemia, suggesting potential independent effects of fibrinogen and IL-6 on type 2 diabetes–related CVD risk in youth.

Although obesity is a major contributor to cardiometabolic risk, prospective studies suggest a possible independent effect of hyperglycemia (22). Hyperglycemia accelerates the formation of advanced glycation end products, which can lead to atherogenic endothelial damage. Our results suggest smaller effects of hyperglycemia, relative to adiposity, on CVD risk profiles in youth with diabetes. However, the present data suggest that hyperglycemia may have important effects on lipoprotein risk factors, including apoB and LDL particle size. Previous data from the SEARCH study indicated that both apoB levels and LDL density increased significantly with increasing A1C in youth with either type 1 or type 2 diabetes (23). Also, insulin therapy in adults with type 2 diabetes was shown to significantly reduce apoB levels (24).

This study has several limitations. The cross-sectional data limits our ability to definitively identify which factors and pathways account for the unfavorable CVD risk profile observed in diabetic youth compared with nondiabetic youth. Also, the case-control design has an inherent limitation of potential selection bias; however, comparisons between eligible type 2 diabetic case subjects that did and did not participate in this study revealed no significant differences in diabetes duration, BMI z-scores, or waist circumference ($P > 0.05$ for each comparison). Additionally, there is a lack of consensus regarding specific criteria and cutoff values for CVD risk factors, particularly in youth. Despite this limitation, our findings that the mean values and prevalence for a majority of CVD risk factors are significantly higher in type 2 diabetic youth is an important and timely observation about the potential burden of comorbidities in this population, especially given that many CVD risk factors encountered in youth track from childhood into adulthood (25).

In summary, when compared with youth without diabetes, type 2 diabetic youth have a higher prevalence of many and multiple CVD risk factors. Adiposity and glycemia are both independent and interdependent contributors to a less favorable CVD risk profile for diabetic youth. Inflammatory and coagulation/prothrombotic factors may also play an important role. Because an earlier age of onset of type 2 diabetes will likely increase the lifetime incidence of CVD complications, early prevention and treatment strategies aimed at reducing the prevalence of CVD risk factors in these youth are needed.

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