Published in final edited form as:

Pediatr Diabetes. 2020 August ; 21(5): 863–870. doi:10.1111/pedi.13021.

The association of low-density lipoprotein cholesterol with elevated arterial stiffness in adolescents and young adults with type 1 and type 2 diabetes: The SEARCH for Diabetes in Youth study

Evgenia Gourgari[1,2], **Jeanette M. Stafford**[3], **Ralph D'Agostino Jr**[3], **Lawrence M. Dolan**[4], **Jean M. Lawrence**[5], **Santica Marcovina**[6], **Lina Merjaneh**[7], **Amy K. Mottl**[8], **Amy S. Shah**[4], **Dana Dabelea**[9]

[1]Division of Pediatric Endocrinology, Department of Pediatrics, Georgetown University, Washington, District of Columbia [2]Section on Endocrinology and Genetics, Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), National Institutes of Health, Bethesda, Maryland [3]Department of Biostatistics and Data Science, Wake Forest School of Medicine, Winston-Salem, North Carolina [4]Division of Endocrinology, Department of Pediatrics, Cincinnati Children's Hospital and the University of Cincinnati, Cincinnati, Ohio [5]Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, California [6]Northwest Lipid Metabolism and Diabetes Research Laboratories, University of Washington, Seattle, Washington [7]Division of Endocrinology, Department of Pediatrics, Seattle Children's Hospital, Seattle, Washington [8]UNC Division of Nephrology and Hypertension, University of North Carolina School of Medicine, Chapel Hill, North Carolina [9]Department of Epidemiology, Colorado School of Public Health, University of Colorado Denver, Aurora, Colorado

Abstract

Aim: Our aim was to explore the relationship of Low-Density Lipoprotein Cholesterol (LDL-C) with subclinical cardiovascular disease (CVD) in youth with T1D and T2D. We hypothesized the association of LDL-C with elevated arterial stiffness (AS) would be partially accounted by the co-occurrence of other CVD factors.

Method: We included 1376 youth with T1D and 157 with T2D from the SEARCH study. CVD risk factors including LDL-C, waist to height ratio (WHtR), mean arterial pressure (MAP), HbA1c, albumin to creatinine ratio (ACR), and insulin sensitivity (IS) score were measured at both visits. At follow up, elevated carotid-femoral AS was defined as levels above 6.8 m/s. Multivariable logistic regression evaluated the odds of elevated AS as a function of the average CVD risk factors.

Results: At follow up, age was 18.0 ± 4.1 and 21.6 ± 3.5 years and duration of diabetes was 7.8 ± 1.9 and 7.7 ± 1.9 years in T1D and T2D, respectively. Elevated AS was found in 8.4% of T1D and 49.0% of T2D participants. Each SD increase in LDL-C was associated with 1.28 increased

Correspondence: Evgenia Gourgari, Georgetown University, Division of Pediatric Endocrinology,4200 Wisconsin Avenue, N.W., 4th Floor, Washington, D.C. 20 016., eg685@georgetown.edu.

odds (95% CI 1.05–1.54, $P = .013$) of elevated AS in youth with T1D. The association was similar but not statistically significant in T2D. WHtR, IS, and MAP were associated with elevated AS in both groups. Adjustment for WHtR or IS attenuated to non-significance the relationship between LDL-C and AS in T1D.

Conclusions: Obesity and insulin resistance attenuate the association of high LDL-C with AS suggesting they partially account for the adverse effects of LDL-C on cardiovascular health in youth with T1D.

Keywords

low-density lipoprotein cholesterol; AS; adolescents; type 1 diabetes; type 2 diabetes; cardiovascular disease; obesity; cholesterol

1 | INTRODUCTION

Youth with type 1 diabetes (T1D) and type 2 diabetes (T2D) have increased risk for cardiovascular disease (CVD).[1] One of the main risk factors for CVD in youth with diabetes is high LDL-C.[1] Prevalence of high LDL-C in youth with diabetes is 15% in T1D and 24% in T2D.[1] In addition to LDL-C, other modifiable cardiovascular risk factors include poor glycemic control, hypertension, obesity and insulin resistance.[1] However, lifestyle modifications in adolescents can be very challenging and the majority do not meet glycemic and weight target.[2–6] It is estimated that only 17% of adolescents with T1D can achieve optimal glycemic control.[1,2,5] Also, 34% of youth with T1D are obese or overweight while 90% of patients with T2D are overweight or obese.[7]

It is important to know how the prolonged presence of modifiable CVD risk factors, such as obesity, hypertension, poor glycemic control, albuminuria, and insulin resistance can affect the relationship of LDL-C with subclinical CVD in youth with diabetes, so that prospective studies can further examine whether interventions that target a lower LDL-C (ie, with aggressive statin use) could be implemented to decrease future CVD complications. Our objective was to explore the relationship of LDL-C with elevated arterial stiffness (AS), a surrogate marker of CVD,[8] after accounting for modifiable CVD risk factors, in youth with T1D and T2D participating in the SEARCH for Diabetes in Youth Cohort Study. We hypothesized the association of LDL-C with elevated arterial stiffness (AS) would be partially accounted by the co-occurrence of other CVD factors.

2 | METHODS

2.1 | Study population

The SEARCH for Diabetes in Youth Cohort study is a longitudinal study following newly diagnosed youth with type 1 or type 2 diabetes in 2002 to 2006 or 2008, who were recruited in five US sites (South Carolina, Cincinnati, Ohio and surrounding counties, Colorado with southwestern Native American sites, Seattle, Washington and surrounding counties, and Kaiser Permanente Southern California members from seven counties).[9]

Participants were recruited for a baseline visit shorty after their diagnosis (on average 9.3 ± 6.4 months from diagnosis). Participants who had at least 5 years of diabetes duration since diagnosis were eligible to participate in the follow-up visit between 2012 and 2015 (on average 7.9 ± 1.9 years from diagnosis) in order to evaluate the presence of subclinical diabetes related complications and comorbidities.[10]

The inclusion criteria for this analysis were (1) baseline and follow-up research visits with a fasting LDL-C, (2) age at least 10 years old at the follow-up visit, and (3) pulse wave velocity measurement at follow-up visit. Exclusion criteria included: (a) reported use of any statin or other lipid-lowering medications during the study period (N = 101) and (b) missing race/ethnicity data (N = 1).

2.2 | Research visits

Local Institutional Review Boards approved the study protocol at each site. Informed consent was obtained from each participant. Research personnel obtained anthropometric measurements, fasting blood samples, and collected questionnaires from participants as previously described.[9,10] Race/ethnicity was self-reported, and it was categorized as non-Hispanic white, Hispanic, non-Hispanic black, American Indian, Asian/Pacific Islander, and other or multiple races/ethnicities. Income and education were self-reported.

The waist was measured at the natural waist location and the waist-to-height ratio was used as a surrogate measurement of adiposity. Systolic and diastolic blood pressure was measured three times at 1-min intervals after at least 5 min of rest and the average value was used in the analysis. Mean Arterial Pressure (MAP) was calculated using the equation MAP = (Systolic Blood Pressure + 2X Diastolic Blood Pressure)/3. The average value for all CVD risk factors (from baseline and follow-up visit) was used in the analysis.

2.3 | Laboratory measures

All participants had a fasting blood draw done after an 8-h fast at both visits. Medications were withheld the day of the visit. Research samples were shipped to the study central laboratory (Northwest Lipid Metabolism and Diabetes Research Laboratories, University of Washington, Seattle, Washington), where low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and HbA1c were measured as previously described.[11] The insulin sensitivity (IS) score was calculated based on a previously described equation validated among SEARCH participants using a euglycemic-hyperinsulinemia clamp[10]: log IS = 4.64725 − 0.02032 (waist, cm) − 0.09779 (HbA1c, %) − 0.00235 (TG, mg/dL). Lower IS score indicates higher insulin resistance. For the urinary albumin to creatinine ratio (ACR), a random urine spot was used.

2.4 | Diabetes type

Diabetes type was defined using an etiologic classification as previously described.[9] Based on this classification, T1D was defined as the presence of at least one positive antibody or a negative antibody but IS score ≥ 8.15.[9,10] T2D was defined as the absence of antibodies and IS score < 8.15. Consequently, there was minimal overlap in IS score ranges between the two groups.

2.5 | AS measures

Carotid to femoral AS measurements were taken only at the follow up visit, using the SphygmoCor Cardiovascular System (AtCor Medical) device, as previously described.[11,12] Higher carotid-femoral PWV indicates elevated AS. Three measurements of carotid-femoral PWV were taken after the participant had rested for 10 min and the results were averaged for these analyses. AS was defined as an elevated PWV above the 90th percentile from a healthy age, sex, and race-ethnicity-matched control group (defined as levels above 6.8 m/s).[9,13] This cut-off level is also in close agreement with the cut-off for elevated PWV described by Elmenhorst et al.[14] (6.03 m/s for men and 5.39 m/s for women who are 21 years of age).

2.6 | Statistical analyses

Descriptive characteristics were summarized using mean (SD) or median (Q1, Q3) for continuous or count (%) for categorical variables. The average value of LDL-C, WHtR, mean arterial pressure, HbA1c, albumin to creatine ratio, and IS from the two visits was used for analysis.

Multivariable logistic regression was used to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) of elevated AS as a function of average levels of CVD risk factors, separately for each diabetes type. Odds ratios were calculated based on a 1-SD increase in LDL-C cholesterol (22.0 mg/dL for type 1 and 29.8 mg/dL for type 2), on 0.05 increase in WHtR, on 5 units increase in MAP, on presence of absence of microalbuminuria defined as above, and on 1 unit increase in IS score. Base models assessed the relationship between LDL-C and elevated AS, adjusting for age, sex, race/ethnicity, diabetes duration, and clinical site (model 1) in all the participants met the eligibility criteria. Sequential models additionally adjusted for WHtR (model 2), MAP (model 3), HbA1c (model 4), ACR (model 5), and IS (model 6) to explore the effect of adjustment for each of the specific CVD risk factor on the relationship between LDL-C and elevated AS.

All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, North Carolina).

3 | RESULTS

3.1 | Descriptive analysis

We identified 1376 youth with T1D and 157 with T2D who were eligible for inclusion in this analysis. The demographic characteristics of youth with T1D and T2D are shown on Table 1. At the follow-up visit, the duration of diabetes was 7.8 ± 1.9 years in T1D youth and 7.7 ± 1.9 years in T2D youth. The average values of cardiovascular risk factors in T1D and T2D are shown in Table 2. Briefly, the average values in T1D were as follows: LDL-C 93.1 ± 2.0 mg/dL, WHtR 0.46 ± 0.05, MAP 78.2 ± 7.6 mmHg, HbA1c 67.9 ± 14.4 mmol/mol (8.4 ± 1.3%), IS 8.8 ± 2.6, and median ACR 7.7 (5.3–13.4). The average values in T2D were: LDL-C 99.4 ± 29.8, WHtR 0.60 ± 0.09, MAP 87.1 ± 7.3 mmHg, HbA1c 67.6 ± 25.4 mmol/mol (8.3 ± 2.3%), IS 4.1 ± 1.6, and median ACR 8.9 (5.2, 23.7).

3.2 | LDL-C and high AS in youth with T1D and T2D

Elevated AS was found in 8.4% of T1D and 49.0% of T2D participants (Table 2). Table 3 includes the results of the multivariable modeling. In youth with T1D, each SD increase in LDL-C was significantly associated with 1.28 increased odds of elevated AS (95% CI: 1.05–1.54, $P = .0126$) after adjusting for age, sex, race/ethnicity, diabetes duration and clinical site (model 1). In individuals with T2D, each SD increase in LDL-C was associated with 1.16 increased odds of elevated AS (95% CI: 0.82–1.63, $P = .4010$) after adjusting for age, sex, race/ethnicity, diabetes duration, and clinical site.

3.3 | Adjusted models for LDL-C and high AS in youth with T1D and T2DM

In the sequential models, we found that WHtR, MAP, and IS were each significantly associated with elevated AS in both T1D and T2D, independent of LDL-C (Table 3 models 2, 3, and 6). Specifically, every 0.05 increase in WHtR (model 2) was associated with 1.72 increased odds of elevated AS (95% CI 1.44–2.05; $P < .001$) in T1D and 2.50 increased odds in T2D (95% CI 1.83–3.41; $P < .0001$). Also, every 5 mmHg increase in MAP (model 3) was associated with 1.63 increased odds of elevated AS (95% CI 1.38–1.92; $P < .001$) in T1D and 1.50 increased odds in T2D (95% CI 1.16–1.95; $P = .0021$). Furthermore, every 1 unit increase in IS score (model 6) was associated with an odds ratio of 0.75 for elevated AS (95% CI 0.68–0.84; $P < .001$) in individuals with T1D and 0.43 (95% CI 0.31–0.58; $P < .001$) in individuals with T2D. HbA1c and urinary ACR were not found to be associated with increased odds of elevated AS in T1D or in T2D, independent of LDL-C. In T1D, after adjustments for either WHtR or IS, the relationship between LDL-C and AS was attenuated and became non-significant (Table 3, models 2 and 6), while the relationship remained significant ($P = .0219$) after adjustment for MAP.

4 | DISCUSSION

The novel findings from these analyses are: (a) LDL-C is significantly associated with 6% higher odds of AS before adjustment for other CVD risk factors in youth with T1D, (b) Waist to height ratio, insulin sensitivity and mean arterial pressure are each independently associated with increased odds of elevated AS in both T1D and T2D, and (c) Waist to height ratio and insulin sensitivity account for the association between LDL-C and AS in youth with T1D.

High LDL-C is a known risk factor for CVD in patients with diabetes and is associated with higher CVD mortality.[1,15] In a relatively young cohort, like SEARCH, hard outcomes such as fatal or non-fatal ischemic heart attacks are rare, and therefore, surrogate measurements of CVD, such as AS, are needed to evaluate CVD burden in youth. Elevated AS has been associated with increased odds of CVD events and mortality in adults and is therefore a validated surrogate measurement of CVD.[8,16]

Elevated AS has been associated with cardiovascular events and mortality in epidemiologic studies in adults,[8,17] therefore, it has been used as a surrogate measure and important biomarker of CVD. In the Framingham Heart Study when individuals in the elevated PWV group were compared to those in the lowest PWV group after adjustment for age, sex, and

standard risk factors, individuals in the highest quartile had an adjusted HR of 3.4 (95% CI, 1.4–8.3; $P = .008$).[8] Elevated arterial stiffness indicates that the arterial wall is stiff, which affects the way blood pressure, blood flow, and arterial diameter change during the cardiac cycle.[18] Furthermore, elevated AS increases the after-load for the left ventricle of the heart, which can lead to ventricular hypertrophy.[19] Our group has previously reported that the age adjusted prevalence of elevated AS is more common in youth with T2D than in T1D.[9,20] Youth with T1D have higher carotid-femoral pulse wave velocity compared to healthy controls.[11] Youth with T2D also have higher carotid-artery AS when compared to obese and lean controls.[21] We have previously shown in a cross-sectional study that age, sex, race, blood pressure, adiposity, and lipid levels are independently associated with AS in T1D.[11] Furthermore, we have shown that increases in LDL-C are associated with higher PWV over time in youth with T1D in the SEARCH-CVD study.[22] This present study expands on previous study in SEARCH by examining the association between LDL-C levels over time and elevated AS, the role of other CVD risk factors over time, and by including both youth with T1D and T2D.

In this analysis, we also showed that in model 1 (adjusted for age, gender, race/ethnicity, DM duration, and clinical site, but none of the other specific CVD risk factors) every 5 mg/dL increase in LDL-C levels over an average period of 7.1 ± 1.9 years, is associated with 6% higher odds of elevated AS in youth with T1D. This is clinically significant, given that approximately 45% of youth with T1D have an LDL-C > 100 mg/dL, which is the recommended LDL-C target for patients with diabetes, and therefore—based on their LDL-C level—are exposed to higher risk for elevated AS.[23] Approximately 12% to 15% of youth age >10 years with T1D have LDL-C above 130 mg/dL.[24] Based on our model, when examining the impact of a 30 mg/dL change in LDL-C we would estimate that youth with T1D and LDL-C above 130 mg/dL, would have 39% increased odds of elevated PWV compared to youth with an LDL-C of 100 mg/dL.

We also showed that (in model 1) every 5 mg/dL increase in average LDL-C levels over an average period of 6.8 ± 2.0 years is associated with 2% higher odds of elevated PWV in youth with T2D. Even though this finding was not statistically significant, likely due, in part, to our smaller sample size in T2D, we believe this is still clinically important, given that approximately 57% of youth with T2D in SEARCH have an LDL-C > 100 mg/dL and 24% have LDL-C above 130 mg/dL.[23] Elevated LDL-C ranging from 24% to 46% have been reported by others in youth with T2D.[25] Based on our model, when examining the impact of a 30 mg/dL change in LDL-C we estimate that youth with T2D and LDL-C above 130 mg/dL, will have a 16% or more increased odds of elevated PWV compared to an LDL-C of 100 mg/dL. Similar to T1D, interventions in T2D youth are also needed in order to minimize this risk. Use of statin medications has been shown to improve cardiovascular outcomes in patients with and without diabetes.[26] In a meta-analysis of 18 686 patients with diabetes a 9% reduction in all-cause mortality per mmol/L reduction in LDL cholesterol was found in participants with diabetes, which was similar to a 13% reduction in participants without diabetes.[26] American Diabetes Association (ADA) recommends the use of statin medications in adults with diabetes aged 40 to 75 years without atherosclerotic disease, regardless of their LDL-C levels.[15] For those who are 20 to 39 years old and have additional CVD risk factors ADA suggests it may be reasonable to initiate a statin.[15] For children with

diabetes the use of statins is recommended for those who, despite lifestyle changes, have an elevated LDL-C > 130 mg/dL and one or more CVD risk factors.[27]

We also found a significant association of waist to height ratio, insulin sensitivity and mean arterial pressure with increased odds of high PWV in both T1D and T2D. Lifestyle and pharmacologic interventions in youth with diabetes try to target obesity, insulin resistance and hypertension in order to improve CVD risk.[28] One third of T1D and 90% of T2D youth are overweight or obese. Also, the age adjusted prevalence of hypertension is 10% in youth with T1D and 21.6% in youth with T2D, and that of albuminuria 5.8% and 19.9%, respectively.[1,9,29] Therefore, youth with diabetes and clinicians should continue focusing on efforts that reduce these CVD risk factors.

In the present analysis, we showed a significant association of average WHtR and IS levels measured over approximately 7 years with elevated PWV, in both T1D and T2D, independent of LDL-C levels. The odds ratio for the effect of elevated WHtR on PWV was somewhat higher in T2D than in T1D (odds ratio 2.5 and 1.7, respectively). This could be explained by the chronic presence of adiposity in youth prior to the diagnosis of T2D which eventually leads to T2D, compared to obesity in T1D which often occurs or worsens after the T1D diagnosis, sometimes as a result of intense insulin treatment.[30,31] Similarly, the protective effect of IS appeared more pronounced in youth with T2D than in youth with T1D (odds ratio of 0.43 vs 0.75, respectively). These results suggest that interventions that ameliorate IS might have more robust CVD benefits in T2D than T1D youth, however both groups could benefit from such interventions. In support of our findings, metformin, which improves insulin sensitivity, has been shown to improve vascular health in obese youth with T1D.[32,33] To the best of our knowledge, there are no randomized controlled studies of metformin in youth with T2D that specifically investigated AS as an outcome. Carefully designed future randomized controlled studies are needed to investigate how interventions that target IS/WHtR and LDL-C could affect the development of elevated AS over time.

After adjusting for either the WHtR or IS, the association of LDL-C with PWV in T1D was no longer significant (Table 3). Our results indicate that the adverse effects of high LCL-C on AS could be partially explained by the co-occurrence of higher WHtR and lower IS levels suggesting that adverse CVD outcomes may be improved by interventions that target obesity and insulin resistance in youth with T1D. Metformin and lifestyle interventions (healthy diet, better sleep hygiene, exercise) that limit weight gain in T1D might also be beneficial. Newer medications such as the GLP-1 agonists, have beneficial effects on obesity and cardiovascular health in adults with T2DM.[34] Whether GLP-1 agonists could also be used for CVD protection in youth with T1D remains to be examined in future studies.

It is also possible that other factors, not tested in our model, which are associated with obesity and insulin resistance could also be responsible for the attenuation of this relationship. Such potential factors could be the lack of exercise, poor sleep hygiene, non-alcoholic fatty liver disease, however our study was not designed to examine these factors. Furthermore, AS is only one, among others, surrogate marker of CVD. It is possible that the relationship of LDL-C with other surrogate markers of CVD is different. In fact, Rodriguez

et al. showed previously that CIMT is indeed independently associated with LDL-C[35] in children with T1D.

We did not find an association of glycemic control with elevated AS, independent of LDL-C levels. Our group has showed before that AS in youth with T1D and T2D is associated with central obesity and high blood pressure but not HbA1c.[20] Taken together, our current findings suggest that while glycemic control is very important to decrease diabetic complications in youth with diabetes in general, obesity, insulin resistance, and high blood pressure may be more important drivers of elevated AS. Unfortunately, obesity and hypertension are not adequately controlled from a young age. In the T1D Exchange cohort, among pediatric patients with T1D and hypertension, only 52% were receiving antihypertensive medications and of those treated, only 32% achieved goal blood pressure.[36] Pediatric diabetes providers often try lifestyle modifications but seldom initiate medications to address hypertension or high cholesterol, even after lifestyle modifications fail.[37] More efforts are needed to align the management of pediatric diabetes with the recommended ADA targets for CVD risk factors.

There are several possible mechanisms pertaining to the patho-physiology of elevated AS in patients with diabetes.[38] One mechanism is the decreased activation of the nitric oxide pathway in the presence of insulin resistance, which may lead to increased vasoconstriction and elevated AS.[39] Another mechanism is the increased production of reactive oxygen species in the environment of insulin resistance, which may contribute to vascular dysfunction and AS.[40] Also, diabetic autonomic neuropathy is characterized by increased sympathetic tone in patients with T1DM which also contributes to elevated arterial tone and AS.[41] Finally, advanced glycation end products can alter the connections of collagen and fibrin and make the arteries stiffer.[42] Although the focus of this manuscript was not to explore the mechanisms of increased AS in T1DM our findings of a significant relationship of insulin sensitivity with elevated AS in youth with diabetes are biologically plausible.

Strengths of our study include a well characterized observational cohort of youth with T1D and T2D with longitudinal measurements of CVD risk factors over time. A limitation of our study is that the AS outcomes were only measured at follow up, so we not able to assess changes in PWV over time. Also, we defined elevated AS based on a cut-off derived from the 90th percentile from healthy lean control group in a matched cohort. We acknowledge that there have been currently no longitudinal studies that have validated this or any other PWV value during childhood with CVD events in adulthood. However, a large systematic review and meta-analysis examined the predictive value of PWV for cardiovascular events by looking at 17 longitudinal studies and a total of 15 877 adult subjects who were followed for an average of 7.7 years.[17] Authors found that an increase in PWV by 1 m/s corresponded to an age-sex-risk factor adjusted risk increase of 14% and 15% in CVD events and mortality, respectively.[17] Our group has published before that the mean carotid-femoral PWV in youth with T1DM was 5.3 ± 0.8 m/s.[13] Data from this large systematic review indicates that youth with T1DM and an elevated AS above 6.8 m/s have at least 15% adjusted increased risk of CVD compared to the average youth with T1DM that has a PWV of 5.3 m/s. Another limitation is the relatively small sample size of youth with T2D, which may have prevented us to detect a statistically significant association of LDL-C with high

PWV that we believe is clinically important. Furthermore, another limitation is that we excluded participants who were treated with statins (N = 101). However, their LDL-C cholesterol level might have been within normal limits on treatment with statins and therefore would be not indicative of the severity of their hyperlipidemia. Finally, we used an estimated measure of IS instead of the gold standard of insulin clamp. However, our equation has been previously validated against the insulin clamp.10

5 | CONCLUSIONS

LDL-C is significantly associated with elevated AS in youth with T1D, but this association is not independent of other CVD risk factors. Specifically, obesity and insulin resistance partially account for the adverse effects of high LDL-C on cardiovascular health in youth with T1D. Future trials should investigate whether interventions that target obesity and insulin sensitivity could improve AS in youth with T1D and T2D and therefore cardiovascular outcomes. Use of statin medications is recommended for patients with markedly elevated LDL-C. Future studies could examine whether the use of statin medications could ameliorate the progression of AS in youth with T1D and T2D.

ACKNOWLEDGMENTS

SEARCH for Diabetes in Youth is funded by the Centers for Disease Control and Prevention (PA numbers 00097, DP-05-069, and DP-10-001) and supported by the National Institute of Diabetes and Digestive and Kidney Diseases. Site Contract Numbers: Kaiser Permanente Southern California (U18DP006133, U48/CCU919219, U01 DP000246, and U18DP002714), University of Colorado Denver (U18DP006139, U48/CCU819241-3, U01 DP000247, and U18DP000247-06A1), Cincinnati's Children's Hospital Medical Center (U18DP006134, U48/CCU519239, U01 DP000248, and 1U18DP002709), University of North Carolina at Chapel Hill (U18DP006138, U48/CCU419249, U01 DP000254, and U18DP002708), Seattle Children's Hospital (U18DP006136, U58/CCU019235-4, U01 DP000244, and U18DP002710-01), Wake Forest University School of Medicine (U18DP006131, U48/CCU919219, U01 DP000250, and 200-2010-35171). The authors wish to acknowledge the involvement of the Kaiser Permanente Southern California' Clinical Research Center (funded by Kaiser Foundation Health Plan and supported in part by the Southern California Permanente Medical Group); the South Carolina Clinical & Translational Research Institute, at the Medical University of South Carolina, NIH/National Center for Advancing Translational Sciences (NCATS) grant number UL1 TR000062, UL1 Tr001450; Seattle Children's Hospital and the University of Washington, NIH/NCATS grant number UL1 TR00423; University of Colorado Pediatric Clinical and Translational Research Center, NIH/NCATS grant Number UL1 TR000154; the Barbara Davis Center at the University of Colorado at Denver (DERC NIH grant number P30 DK57516); the University of Cincinnati, NIH/NCATS grant number UL1 TR000077, UL1 TR001425; and the Children with Medical Handicaps program managed by the Ohio Department of Health. This study includes data provided by the Ohio Department of Health, which should not be considered an endorsement of this study or its conclusions. Dr. Gourgari has support from a KL2: Award Numbers KL2TR001432 and UL1TR001409 from the National Center for Advancing Translational Science. The SEARCH for Diabetes in Youth Study is indebted to the many youth and their families, and their health care providers, whose participation made this study possible.

Funding information

Dr. Gourgari has support from a KL2: Award Numbers KL2TR001432 and UL1TR001409 from the National Center for Advancing Translational Science.; SEARCH for Diabetes in Youth is funded by the Centers for Disease Control and Prevention (PA numbers 00097, DP-05-069, and DP-10-001) and supported by the National Institute of Diabetes and Digestive and Kidney Diseases.

REFERENCES

1. Maahs DM, Daniels SR, de Ferranti SD, et al. Cardiovascular disease risk factors in youth with diabetes mellitus: a scientific statement from the American Heart Association. Circulation. 2014;130(17):1532–1558. [PubMed: 25170098]

2. Miller KM, Foster NC, Beck RW, et al. Current state of type 1 diabetes treatment in the U.S.: updated data from the T1D Exchange clinic registry. Diabetes Care. 2015;38(6):971–978. [PubMed: 25998289]

3. McGavock J, Dart A, Wicklow B. Lifestyle therapy for the treatment of youth with type 2 diabetes. Curr Diab Rep. 2015;15(1):568. [PubMed: 25398207]

4. Minges KE, Whittemore R, Grey M. Overweight and obesity in youth with type 1 diabetes. Annu Rev Nurs Res. 2013;31:47–69. [PubMed: 24894137]

5. Petitti DB, Klingensmith GJ, Bell RA, et al. Glycemic control in youth with diabetes: the SEARCH for diabetes in youth study. J Pediatr. 2009;155(5):668–672. [PubMed: 19643434]

6. Pinto CA, Stafford JM, Wang T, et al. Changes in diabetes medication regimens and glycemic control in adolescents and young adults with youth-onset type 2 diabetes: the SEARCH for Diabetes in Youth study. Pediatr Diabetes. 2018;19:1065–1072.

7. Liu LL, Lawrence JM, Davis C, et al. Prevalence of overweight and obesity in youth with diabetes in USA: the SEARCH for diabetes in youth study. Pediatr Diabetes. 2010;11(1):4–11. [PubMed: 19473302]

8. Mitchell GF, Hwang SJ, Vasan RS, et al. Arterial stiffness and cardiovascular events: the Framingham heart study. Circulation. 2010;121(4):505–511. [PubMed: 20083680]

9. Dabelea D, Stafford JM, Mayer-Davis EJ, et al. Association of Type 1 diabetes vs type 2 diabetes diagnosed during childhood and adolescence with complications during teenage years and young adulthood. JAMA. 2017;317(8):825–835. [PubMed: 28245334]

10. Dabelea D, D'Agostino RB Jr, Mason CC, et al. Development, validation and use of an insulin sensitivity score in youths with diabetes: the SEARCH for diabetes in youth study. Diabetologia. 2011;54(1): 78–86. [PubMed: 20886205]

11. Shah AS, Wadwa RP, Dabelea D, et al. Arterial stiffness in adolescents and young adults with and without type 1 diabetes: the SEARCH CVD study. Pediatr Diabetes. 2015;16(5):367–374. [PubMed: 25912292]

12. Jaiswal M, Urbina EM, Wadwa RP, et al. Reduced heart rate variability among youth with type 1 diabetes: the SEARCH CVD study. Diabetes Care. 2013;36(1):157–162. [PubMed: 22961570]

13. Urbina EM, Wadwa RP, Davis C, et al. Prevalence of increased arterial stiffness in children with type 1 diabetes mellitus differs by measurement site and sex: the SEARCH for diabetes in youth study. JPediatr. 2010;156(5):731–737. [PubMed: 20097360]

14. Elmenhorst J, Hulpke-Wette M, Barta C, Dalla Pozza R, Springer S, Oberhoffer R. Percentiles for central blood pressure and pulse wave velocity in children and adolescents recorded with an oscillometric device. Atherosclerosis. 2015;238(1):9–16. [PubMed: 25461733]

15. American Diabetes Association. 10. Cardiovascular disease and risk management: standards of medical Care in Diabetes-2020. Diabetes Care. 2020;43(suppl 1):S111–S134. [PubMed: 31862753]

16. Said MA, Eppinga RN, Lipsic E, Verweij N, van der Harst P. Relationship of arterial stiffness index and pulse pressure with cardiovascular disease and mortality. J Am Heart Assoc. 2018;7(2):e007621. [PubMed: 29358193]

17. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol. 2010;55(13):1318–1327. [PubMed: 20338492]

18. Townsend RR, Wilkinson IB, Schiffrin EL, et al. Recommendations for improving and standardizing vascular research on arterial stiffness: a scientific statement from the American Heart Association. Hypertension. 2015;66(3):698–722. [PubMed: 26160955]

19. Nichols WW. Clinical measurement of arterial stiffness obtained from noninvasive pressure waveforms. Am J Hypertens. 2005;18(1 Pt 2): 3S–10S. [PubMed: 15683725]

20. Wadwa RP, Urbina EM, Anderson AM, et al. Measures of arterial stiffness in youth with type 1 and type 2 diabetes: the SEARCH for Diabetes in Youth study. Diabetes Care. 2010;33(4):881–886. [PubMed: 20067960]

21. Urbina EM, Kimball TR, Khoury PR, Daniels SR, Dolan LM. Increased arterial stiffness is found in adolescents with obesity or obesity-related type 2 diabetes mellitus. J Hypertens. 2010;28(8):1692–1698. [PubMed: 20647860]

22. Dabelea D, Talton JW, D'Agostino R Jr, et al. Cardiovascular risk factors are associated with increased arterial stiffness in youth with type 1 diabetes: the SEARCH CVD study. Diabetes Care. 2013;36(12): 3938–3943. [PubMed: 24101697]
23. Kershnar AK, Daniels SR, Imperatore G, et al. Lipid abnormalities are prevalent in youth with type 1 and type 2 diabetes: the SEARCH for diabetes in youth study. J Pediatr. 2006;149(3):314–319. [PubMed: 16939739]
24. Glaser NS, Geller DH, Haqq A, Gitelman S, Malloy M, on behalf of the Lawson Wilkins Pediatric Endocrine Society Committee on Drugs and Therapeutics. Detecting and treating hyperlipidemia in children with type 1 diabetes mellitus: are standard guidelines applicable to this special population? Pediatr Diabetes. 2011;12(4 Pt 2):442–459. [PubMed: 21054719]
25. Pinhas-Hamiel O, Zeitler P. Acute and chronic complications of type 2 diabetes mellitus in children and adolescents. Lancet. 2007;369 (9575):1823–1831. [PubMed: 17531891]
26. Cholesterol Treatment Trialists Kearney PM, Blackwell L, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet. 2008;371 (9607):117–125. [PubMed: 18191683]
27. American Diabetes Association. 13. Children and adolescents: standards of medical Care in Diabetes-2020. Diabetes Care. 2020;43 (Suppl 1):S163–S182. [PubMed: 31862756]
28. Gourgari E, Dabelea D, Rother K. Modifiable risk factors for cardiovascular disease in children with type 1 diabetes: can early intervention prevent future cardiovascular events? Curr Diab Rep. 2017;17(12):134. [PubMed: 29101482]
29. Schwab KO, Doerfer J, Hecker W, et al. Spectrum and prevalence of atherogenic risk factors in 27,358 children, adolescents, and young adults with type 1 diabetes: cross-sectional data from the German diabetes documentation and quality management system (DPV). Diabetes Care. 2006;29(2):218–225. [PubMed: 16443863]
30. Maffeis C, Birkebaek NH, Konstantinova M, et al. Prevalence of underweight, overweight, and obesity in children and adolescents with type 1 diabetes: data from the international SWEET registry. Pediatr Diabetes. 2018;19(7):1211–1220. [PubMed: 30033651]
31. De Keukelaere M, Fieuws S, Reynaert N, et al. Evolution of body mass index in children with type 1 diabetes mellitus. Eur J Pediatr. 2018;177(11):1661–1666. [PubMed: 30091111]
32. Bjornstad P, Schafer M, Truong U, et al. Metformin improves insulin sensitivity and vascular health in youth with type 1 diabetes mellitus. Circulation. 2018;138(25):2895–2907. [PubMed: 30566007]
33. Anderson JJA, Couper JJ, Giles LC, et al. Effect of metformin on vascular function in children with type 1 diabetes: a 12-month randomized controlled trial. J Clin Endocrinol Metab. 2017;102(12):4448–4456. [PubMed: 29040598]
34. Dey AK, Groenendyk J, Mehta NN, Gourgari E. The effect of sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide 1 agonists on cardiovascular disease in patients with type 2 diabetes. Clin Cardiol. 2019;42(3):406–412. [PubMed: 30635924]
35. Rabago Rodriguez R, Gomez-Diaz RA, Tanus Haj J, et al. Carotid intima-media thickness in pediatric type 1 diabetic patients. Diabetes Care. 2007;30(10):2599–2602. [PubMed: 17644614]
36. Nambam B, DuBose SN, Nathan BM, et al. Therapeutic inertia: under-diagnosed and undertreated hypertension in children participating in the T1D exchange clinic registry. Pediatr Diabetes. 2016;17(1):15–20. [PubMed: 25330905]
37. Katz ML, Guo Z, Laffel LM. Management of hypertension and high low-density lipoprotein in pediatric type 1 diabetes. J Pediatr. 2018; 197:140–146. [PubMed: 29395184]
38. Urbina EM, Isom S, Bell RA, et al. Burden of cardiovascular risk factors over time and arterial stiffness in youth with type 1 diabetes mellitus: the SEARCH for diabetes in youth study. J Am Heart Assoc. 2019;8(13):e010150. [PubMed: 31213111]
39. Eringa EC, Stehouwer CD, Roos MH, Westerhof N, Sipkema P. Selective resistance to vasoactive effects of insulin in muscle resistance arteries of obese Zucker (fa/fa) rats. Am J Physiol Endocrinol Metab. 2007;293(5):E1134–E1139. [PubMed: 17623751]
40. Muniyappa R, Iantorno M, Quon MJ. An integrated view of insulin resistance and endothelial dysfunction. Endocrinol Metab Clin North Am. 2008;37(3):685–711. [PubMed: 18775359]

41. Prince CT, Secrest AM, Mackey RH, Arena VC, Kingsley LA, Orchard TJ. Cardiovascular autonomic neuropathy, HDL cholesterol, and smoking correlate with arterial stiffness markers determined 18 years later in type 1 diabetes. Diabetes Care. 2010;33(3):652–657. [PubMed: 20040653]

42. Aronson D Cross-linking of glycated collagen in the pathogenesis of arterial and myocardial stiffening of aging and diabetes. J Hypertens. 2003;21(1):3–12. [PubMed: 12544424]

TABLE 1

Demographic characteristics of 1533 adolescents and young adults at follow-up visit by diabetes type: the SEARCH for Diabetes in Youth study

	Mean ± SD	
Variable	**T1D (*N* = 1376)**	**T2D (*N* = 157)**
Age	18.0 ± 4.1	21.6 ± 3.5
Duration of diabetes (years)	7.8 ± 1.9 Count (%)	7.7 ± 1.9
Sex		
Female	680 (49.4)	102 (65.0)
Male	696 (50.6)	55 (35.0)
Race		
Non-Hispanic white	1062 (77.2)	46 (29.3)
Other race/ethnic group	314 (22.8)	111 (70.7)
Income		
<$25K	206 (15.0)	61 (39.4)
$25–49K	230 (16.8)	27 (17.4)
$50–74K	214(15.6)	11 (7.1)
$75K+	499 (36.4)	9 (5.8)
Do not know/refused	221 (16.1)	47 (30.3)
Insurance		
None	52 (3.8)	29 (19.6)
Other	62 (4.5)	13 (8.8)
Medicaid/Medicare	272 (19.9)	55 (37.2)
Private	983 (71.8)	51 (34.5)

Note: Table entries are mean ± SD for continuous or count (%) for categorical data.

Abbreviations: T1D, type 1 diabetes; T2D, type 2 diabetes.

TABLE 2

CVD risk factors in adolescents and young adults with T1D and T2D

	Mean ± SD	
Variable	**T1D (*N* = 1376)**	**T2D (*N* = 157)**
LDL-C (mg/dL)	93.1 ± 22.0	99.4 ± 29.8
WHtR	0.46 ± 0.05	0.60 ± 0.09
MAP (mmHg)	78.2 ± 7.6	87.1 ± 7.3
HbA1c (%)	8.4 ± 1.3	8.3 ± 2.3
HbAa1c (mmol/mol)	67.9 ± 14.4	67.6 ± 25.4
ACR (median [Q1, Q3])	7.7 (5.3, 13.4)	8.9 (5.2, 23.7)
ACR ≥ 30 (count [%])	140 (10.4)	35 (22.9)
IS score	8.8 ± 2.6	4.1 ± 1.6
PWV (m/s)[a]	5.5 ± 1.0	6.9 ± 1.4
Elevated AS[b] (count [%])	116 (8.4)	77 (49.0)

Note: Table entries are mean ± SD unless otherwise indicated. Data are the mean of baseline and follow-up values except the PWV which was only measured at the follow up visit.

Abbreviations: T1D, type 1 diabetes; T2D, type 2 diabetes; LDL-C, LDL-cholesterol; WHtR, waist to height ratio; MAP, mean arterial pressure; ACR, albumin to creatinine ratio; IS score, insulin sensitivity score; PWV, pulse wave velocity.

[a]One high outlier winsorized to the next highest value in the analysis dataset.

[b]Cut point based on 90th percentile from CVD control group (6.8 m/s for PWV).

TABLE 3

Odds ratios and 95% CIs for the association between LDL cholesterol, other CVD risk factors and elevated[a] AS in youth with T1D and T2D

	N with elevated AS	CVD risk factor estimate OR (95% CI)[b]	CVD risk factor *P* value	LDL-C [1-SD increase (22.0 mg/dL for type 1 and 29.8 mg/dL for type 2)] OR (95% CI)[b]	LDL-C *P* value
Type 1 diabetes (*N* = 1376)					
Model 1[c] LDL-C	116	-	-	1.28 (1.05, 1.54)	.013
Model 2: M1 + WHtR (per 0.05)	116	1.72 (1.44, 2.05)	<.0001	1.15 (0.94, 1.41)	.174
Model 3: M1 + MAP (per 5 units)	116	1.63 (1.38, 1.92)	<.0001	1.26 (1.03, 1.53)	.022
Model 4: M1 + HbA1c (per 1unit)	116	1.05 (0.91, 1.21)	.4783	1.26 (1.04, 1.53)	.018
Model 5: M1 + microalbuminuria[d] (*N* = 1348)	114	1.12 (0.59, 2.13)	.7189	1.28 (1.06, 1.55)	.011
Model 6: M1 + IS (per 1 unit)	116	0.75 (0.68, 0.84)	<.0001	1.13 (0.93, 1.37)	.237
Type 2 diabetes (*N* = 157)					
Model 1[c]: no added risk factor	77	-	-	1.16 (0.82, 1.63)	.401
Model 2: M1 + WHtR (per 0.05)	77	2.50 (1.83, 3.41)	<.0001	1.33 (0.88, 2.01)	.183
Model 3: M1 + MAP (per 5 units)	77	1.50 (1.16, 1.95)	.0021	1.17 (0.82, 1.65)	.390
Model 4: M1 + HbA1c (per 1 unit)	77	0.90 (0.77, 1.06)	.2217	1.26 (0.87, 1.83)	.216
Model 5: M1 + microalbuminuria[d] (*N* = 153)	76	1.49 (0.65, 3.38)	.3446	1.21 (0.85, 1.73)	.283
Model 6: M1 + IS (per 1 unit)	77	0.43 (0.31, 0.58)	<.0001	0.82 (0.54, 1.25)	.367

Abbreviations: T1D, type 1 diabetes; T2D, type 2 diabetes; WHtR, waist to height ratio; MAP, mean arterial pressure; ACR, albumin to creatinine ratio; IS, insulin sensitivity score.

[a]Cut point for elevated AS is based on 90th percentile from SEARCH CVD control group as a pulse wave velocity >6.8 m/s.

[b]Odds ratios were calculated based on a 1-SD increase in LDL-C cholesterol (22.0 mg/dL for type 1 and 29.8 mg/dL for type 2), on 0.05 increase in WHtR, on 5 units increase in MAP, on presence of absence of microalbuminuria defined as above, and on 1 unit increase in IS score.

[c]Model 1 includes age, gender, race/ethnicity, and DM duration. All models are also adjusted for clinical site.

[d] Microalbuminuria was defined as ACR ≥ 30 (positive) vs <30 mg/dL (negative).