Early Atherosclerosis Relates to Urinary Albumin Excretion and Cardiovascular Risk Factors in Adolescents With Type 1 Diabetes: Adolescent Type 1 Diabetes cardio-renal Intervention Trial (AdDIT)

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OBJECTIVE

The origins of cardiovascular and renal disease in type 1 diabetes begin during childhood. We aimed to evaluate carotid (cIMT) and aortic intima-media thickness (aIMT) and their relationship with cardiovascular risk factors and urinary albumin excretion in adolescents with type 1 diabetes in the Adolescent Type 1 Diabetes cardio-renal Intervention Trial (AdDIT).

RESEARCH DESIGN AND METHODS

A total of 406 adolescents with type 1 diabetes, who were 14.1 ± 1.9 years old with type 1 diabetes duration of 6.7 ± 3.7 years, and 57 age-matched control subjects provided clinical and biochemical data and ultrasound measurements of vascular structure (cIMT and aIMT). Vascular endothelial and smooth muscle function was also measured in 123 of 406 with type 1 diabetes and all control subjects.

RESULTS

In type 1 diabetic subjects, mean/maximal aIMT ($P < 0.006$; <0.008), but not mean/maximal cIMT, was greater than in control subjects. Mean/maximal aIMT related to urinary albumin-to-creatinine ratio (multiple regression coefficient [SE], 0.013 [0.006], $P = 0.03$; 0.023 [0.007], $P = 0.002$), LDL cholesterol (0.019 [0.008], $P = 0.02$; 0.025 [0.011], $P = 0.02$), and age (0.010 [0.004], $P = 0.004$; 0.012 [0.005], $P = 0.01$), independent of other variables. Mean/maximal cIMT was greater in males (0.023 [0.006], $P = 0.02$; 0.029 [0.007], $P < 0.0001$), and mean cIMT related independently to systolic blood pressure (0.001 [0.001], $P = 0.04$). Vascular smooth muscle function related to aIMT and cIMT but not to urinary albumin excretion.

CONCLUSIONS

aIMT may be a more sensitive marker of atherosclerosis than cIMT in type 1 diabetes during mid-adolescence. Higher urinary albumin excretion, even within the normal range, is associated with early atherosclerosis and should direct clinical attention to modifiable cardiovascular risk factors.

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Children with type 1 diabetes are at greatly increased risk for the development of both renal and cardiovascular disease in later life (1,2). Evidence is accumulating that these two complications may have a common pathophysiology, with endothelial dysfunction a key early event.

Microalbuminuria is a recognized marker of endothelial damage (3) and predicts progression to proteinuria and diabetic nephropathy, as well as to atherosclerosis (4) and increased cardiovascular risk (5). It is, however, rare in adolescents with type 1 diabetes who more often have higher urinary albumin excretion rates within the normal range, which are associated with later progression to microalbuminuria and proteinuria (6). Renal decline may, however, precede microalbuminuria, at least in adults with type 1 diabetes (7,8), and the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study irrefutably confirms the importance of intensive therapy to reduce risk at each stage of the progression to proteinuria (9).

The Adolescent Type 1 Diabetes cardiorenal Intervention Trial (AdDIT) (10) is designed to examine the impact of minor differences in albumin excretion in adolescents on the initiation and progression of cardiovascular and renal disease. The primary cardiovascular end point in AdDIT is carotid intima-media thickness (cIMT). Subclinical atherosclerosis can be detected noninvasively using high-resolution ultrasound to measure the intima-media thickness (IMT) of the carotid arteries, which predicts cardiovascular morbidity and mortality (11,12). Whereas cIMT is increased by late adolescence and during early adulthood in type 1 diabetes (13), this finding is inconsistent in earlier childhood, when the first changes of atherosclerosis begin. Autopsy studies in children show that the earliest atherosclerotic changes (fatty streaks) occur in the distal abdominal aortic wall (14); aorta IMT (aIMT) is measurable and increased in children and adolescents with type 1 diabetes (15,16). It is also possible that drivers of atherosclerosis differ between different vascular beds.

The primary aim of this study was to examine the relationship of increased urinary albumin excretion and cardiovascular risk factors in adolescents with type 1 diabetes with structural arterial wall changes. We hypothesized that even minor increases in albumin excretion would be associated with early atherosclerosis but that this would be detectable only in the abdominal aorta. Secondary aims were to compare cIMT and aIMT in type 1 diabetes and control subjects and in a subgroup examine the relationship of vascular endothelial and smooth muscle function with IMT and urinary albumin excretion.

RESEARCH DESIGN AND METHODS

Subjects and Study Design

A total of 406 adolescents, aged 10–16 years, with type 1 diabetes for more than 1 year, recruited in five centers across Australia, were enrolled in this cross-sectional study (Table 1). Some participants (n = 337) had been screened for urinary albumin excretion as part of AdDIT, a multicenter multinational (U.K., Canada, and Australia) randomized controlled trial (clinical trial reg. no. ISRCTN91419926) (10). An additional 69 participants were not screened for the AdDIT study but were recruited using the same inclusion criteria and investigations, except for having one early morning urinary albumin-to-creatinine ratio (ACR) only.

The AdDIT screening measured ACR in two sets of three consecutive early-morning urine samples. The two screening visits showed a close correlation, and the median of the six urinary ACR measurements was used in analysis (17).

Exclusion criteria were other types of diabetes without detected islet autoantibodies at diagnosis, severe hyperlipidemia and/or familial hypercholesterolemia, hypertension, exposure to ACE inhibitors or statins, other comorbidities considered unsuitable by the investigator (excluding treated hypothyroidism and celiac disease), and proliferative retinopathy.

Healthy age- and sex-matched control subjects (n = 57) were recruited at the central site, Adelaide, South Australia, from relatives and school friends of the participants with type 1 diabetes. They had the same clinical, biochemical, and ultrasound assessments. They were compared with 167 adolescents with type 1 diabetes for IMT and 123 adolescents with type 1 diabetes for flow-mediated dilatation (FMD) and glyceryl trinitrate–mediated dilatation (GTN), and all had their images measured on the same ultrasound machine in Adelaide.

The study was approved by the Human Research Ethics Committee of each of the five participating centers in Australia. Written informed consent was obtained from all parents/guardians and the study participants.

Clinical Assessments

All participants were required to be well without fever, intercurrent infection, or

Table 1—Characteristics of adolescents with type 1 diabetes and control subjects

	Type 1 diabetic subjects	Control subjects	P
n	406	57	
Age (years)	14.2 ± 1.9	14.0 ± 2.9	0.6
Diabetes duration (years)	6.7 ± 3.7	—	—
BMI (kg/m^2)	22.0 ± 3.6	20.9 ± 4.1	0.03
BMI z score	0.61 ± 0.8	0.34 ± 0.96	0.02
Waist circumference (cm)	74.3 ± 9.1	71.3 ± 9.2	0.03
Mean SBP (mmHg)	117.1 ± 12.0	109.6 ± 7.4	<0.0001
Mean DBP (mmHg)	65.7 ± 7.6	60.8 ± 6.1	<0.0001
HbA_{1c} (%, mmol/mol)	8.5 ± 1.4, 69 ± 11.4	5.2 ± 0.3, 33 ± 1.9	<0.0001
Total cholesterol (mmol/L)	4.5 ± 0.9	4.0 ± 0.7	<0.0001
HDL cholesterol (mmol/L)	1.56 ± 0.35	1.46 ± 0.34	0.05
Triglycerides (mmol/L)	1.05 ± 0.71	0.78 ± 0.34	0.01
LDL cholesterol (mmol/L)	2.42 ± 0.75	2.17 ± 0.57	0.02
eGFR (mL/min/1.73 m^2)	128.79 ± 24.75	—	—
Urinary ACR (mg/mmol)	1.03 ± 0.95	—	—
Race (% European/Asian/other)	91/6/3	93/7/0	0.7

Data are means ± SD unless otherwise indicated.

ketosis on the days of investigation. Data on age, duration of diabetes, anthropometry (weight, height, and waist circumference), pubertal (Tanner) stage, and blood pressure were collected. Height was measured on wall-mounted stadiometers and weight on electronic scales. Waist circumference was measured in triplicate with a flexible tape at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest following World Health Organization guidelines.

Brachial blood pressure was measured three times (Omran M6 Blood Pressure Monitor; Kyoto), separated by 5-min intervals using the appropriate cuff size. The average of the three measurements was used in the analysis. The cuff was chosen to be of the appropriate size for the adolescents' upper arm, with a bladder width that was at least 40% of the arm circumference at a point midway between the olecranon and the acromion and a bladder length to cover 80–100% of the circumference of the arm.

A blood sample was collected for HbA_{1c} and lipid profile (total cholesterol, triglycerides, HDL cholesterol, and LDL cholesterol) measurement at the local laboratories.

Ultrasound Assessment of Vascular Structure and Function

Ultrasound images of vascular structure (aIMT and cIMT) were collected at five Australian vascular centers by accredited vascular sonographers. All images were read at the central site in Adelaide. Reproducibility and quality control among the measurements of IMT in each center and between centers were ensured as follows: *1*) sonographer training conducted through the Vascular Imaging Unit at the Women and Children's Hospital, Adelaide, which has extensive experience over 15 years in running vascular health studies in children; *2*) intrasonographer reproducibility on scans produced on two separate occasions in the same five subjects for aIMT was 2.8% and on scans produced on two separate occasions in the same 13 subjects for cIMT was 3.6%; *3*) three trial images were sent and assessed for quality before the sonographer was accredited to be part of the study; *4*) all images were read by one of two independent observers (O.M. and M. La Forgia) at the central site who were blinded to the subjects' clinical characteristics; and *5*) intraobserver coefficient of variation (CV) in 33 subjects, within this cohort, was 0.6% for cIMT and 1.4% for aIMT, and interobserver CV in 20 subjects, within this cohort, was 1.8% for cIMT and 2.3% for aIMT.

Ultrasound images of left and right common carotid arteries and abdominal aorta were acquired using our standardized protocol (16). For cIMT, images of the posterior wall of the distal 10-mm-long arterial segment of the common carotid artery, just 1 cm proximal to the carotid bulb, were recorded. For aIMT, images of the straight, most distal 10 mm of the abdominal aorta just before the bifurcation were recorded. A minimum of three images at end diastole, triggered on the R wave of the electrocardiogram (ECG), for each of the common carotid arteries and abdominal aorta was taken and digitally stored for later analysis. The greatest distance between the lumen-intima interface and media-adventitia interface was measured at a minimum of 100 points using a semiautomated edge detection and measurement computer software package (B. Bailey; Royal Prince Alfred Hospital, NSW, Australia). Three best quality images for cIMT (right and left carotids) and aIMT were selected and analyzed for mean and maximal IMT. The mean of the readings was recorded to give the final result for each subject.

Ultrasound assessments of vascular endothelial function measured by FMD and vascular smooth muscle function measured by GTN were performed at the central site only. FMD and GTN were assessed as previously described (18). Brachial artery diameter was measured in a longitudinal section 2–15 cm above the elbow using B mode ultrasound with a 17-MHz linear array transducer (Philips iU22; Philips, Bothell, WA). An ECG was recorded simultaneously with the ultrasound images. Each study included four scans: *1*) a resting scan, after which reactive hyperemia was induced by occluding arterial blood flow using a sphygmomanometer inflated to 250 mmHg for 4 min; *2*) an FMD scan recorded between 45 and 75 s after cuff deflation; *3*) a recontrol scan 10–15 min later; and *4*) the last scan, taken 4 min after the sublingual administration of the GTN spray (400 μg; Nitrolingual Pump spray, Sanofi). For each scan, measurements were made over four consecutive cardiac cycles, incident with the R wave on the ECG, by observers blinded to the subject group using ultrasonic calipers. Measurements were averaged and expressed as percentages of the resting vessel diameter. Interobserver CV between 20 subjects studied on two occasions was 3.9% for FMD and 4.0% for GTN (18).

Biochemical Assessments

In AdDIT participants, urinary biochemical assessments were performed in a central laboratory (WellChild Laboratory, London, U.K.). Urine albumin was measured using nephelometric immunoassay (Siemens BN Prospec). Urine albumin concentrations below the limit of quantitation of nephelometry, <2.1 mg/L, were measured using ELISA. Between-batch imprecision for the BN Prospec was 3.7% at 4.16 mg/L (n = 51), 2.9% at 19.0 mg/L (n = 55), and 2.9% at 144 mg/L (n = 54). Between-batch imprecision on the ELISA at <2.1 mg/L was $<15\%$. Urine creatinine was measured using a chromatographic stable isotope dilution electrospray mass spectrometry–mass spectrometry method on an AB SCIEX API5000. Between-batch imprecision (n = 48) was 2.6% at 6.89 mmol/L and 3.3% at 17.4 mmol/L. Plasma creatinine was measured using a reference stable isotope dilution electrospray mass spectrometry–mass spectrometry.

In those 69 of 406 subjects who were not screened for AdDIT, urinary albumin was measured by an immunoturbidimetric assay and urinary creatinine by an enzyme colorimetric method (Roche Cobas C501; Hitachi) at the Adelaide site. There was a close correlation between measurements performed in London and Adelaide in 106 samples (r = 0.99 [$P < 0.0001$], 0.81 [$P < 0.0001$], and 0.99 [$P < 0.0001$] for albumin, creatinine, and ACR, respectively).

Lipids were measured using commercial enzymatic assays on Roche Hitachi cobas C systems. HbA_{1c} was assessed in the five local laboratories using a Vantage analyzer (Siemens Diagnostics, Camberley, U.K.), or a Variant analyzer (Bio-Rad Laboratories, Hercules, CA), both of which showed high correlations with DCCT-standardized control subjects (r = 0.98).

Calculations

BMI was calculated as weight in kilograms divided by the square of height in meters, and *z* scores were calculated using the Centers for Disease Control and Prevention, National Center for Health Statistics 2000 growth charts, U.S. (19). Estimated glomerular filtration rate (eGFR) (milliliters per minute per 1.73 meters squared) was calculated as 42 × height (centimeters)/plasma creatinine (micromoles per liter).

Statistical Analysis

Data are summarized as mean ± SD. Clinical characteristics (Table 1) were compared between groups using independent-sample *t* tests and χ^2 tests as appropriate. Univariable linear regression models were used to identify predictors of each IMT outcome in adolescents with type 1 diabetes. Variables that were statistically significant ($P < 0.05$) on univariable analysis and that had data available on >75% of observations (all except for GTN and eGFR) were entered into multivariable models for each IMT outcome in order to identify independent predictors of the respective outcome. To avoid potential issues with multicollinearity, BMI (correlated with waist circumference) and total cholesterol (correlated with LDL cholesterol) were not considered for inclusion into multivariable models. Comparisons of the four IMT outcomes (mean/maximal cIMT and mean/maximal aIMT) between the adolescents with type 1 diabetes and control subjects were performed using simple linear regression models.

Two-tailed *P* values <0.05 were considered statistically significant. Statistical analyses were performed using SAS, version 9.3 (SAS Institute, Cary, NC).

RESULTS

Subject Characteristics

A total of 406 adolescents (211 boys) with type 1 diabetes (47 from New South Wales, 35 from Queensland, 167 from South Australia, 75 from Victoria, and 82 from Western Australia) and 57 healthy adolescents (26 boys) from South Australia were included in the analysis (Table 1). There were no significant clinical or biochemical differences between the type 1 diabetic subjects screened for AdDIT (*n* = 337) and the rest of the type 1 diabetic group (*n* = 69) (data not shown).

Some (21.7%) of the adolescents with type 1 diabetes met the target metabolic control (HbA_{1c} <7.5%), and 135 of 406 (33.3%) adolescents with type 1 diabetes and 14 of 57 (24.5%) control subjects ($P < 0.05$) were overweight or obese (BMI >85th centile for sex and age). Pubertal staging by self-report in 347 of 406 type 1 diabetic subjects showed that 11% were Tanner stage 1, 55% Tanner 2–4, and 34% Tanner 5.

Associations With IMT

aIMT and cIMT was measurable in 92% and 100% of the subjects studied, respectively.

aIMT

Mean/maximal aIMT in 373 subjects with type 1 diabetes was 0.61 ± 0.11/0.76 ± 0.16 mm. Univariable analysis showed that older subjects and those with longer diabetes duration, greater waist circumference, higher systolic (SBP) and diastolic blood pressure (DBP), LDL cholesterol and ACR, and lower GTN had greater mean and maximal aIMT. In the multivariable analysis, mean and maximal aIMT were independently associated with age, LDL cholesterol, and ACR (Table 2). An increase in ACR by 1 unit was associated with a significant increase in mean aIMT by 0.013 mm and an increase in maximal aIMT by 0.023 mm, independent of age, diabetes duration, waist circumference, blood pressure, LDL cholesterol, and center effect. The significant relationship between ACR and mean/maximal aIMT was not altered by excluding the 69 participants who had only one ACR measurement.

cIMT

Mean/maximal cIMT in 397 subjects with type 1 diabetes (nine subjects had aIMT images collected only) was 0.49 ± 0.08/0.59 ± 0.09 mm. Univariable analysis showed that males and those with longer diabetes duration, greater waist circumference, higher SBP and DBP, higher HbA_{1c}, higher eGFR, and lower GTN had greater mean and maximal cIMT. In the multivariable analysis, mean and maximal cIMT were independently associated with sex, and mean cIMT independently associated with SBP (Table 3). As for aIMT, center effect was included in the multivariable analysis (Tables 2,3). In type 1 diabetes, mean cIMT related to mean aIMT ($r = 0.37$, $P < 0.0001$) and maximal cIMT related to maximal aIMT ($r = 0.41$, $P < 0.0001$).

IMT in Type 1 Diabetic Versus Control Subjects

Adolescents with type 1 diabetes in whom IMT images were taken on the one ultrasound machine at the Adelaide central site (*n* = 167) had greater aIMT, but not cIMT, than healthy age- and sex-matched control subjects (*n* = 57) (Table 4). Respectively, 60.7% and 61.3% of adolescents with type 1 diabetes had mean/maximal aIMT above the control mean; 52.1% and 55.1% had mean/maximal cIMT above the control mean.

Vascular Endothelial and Smooth Muscle Function

FMD and GTN were lower in type 1 diabetic than control subjects (Table 4). Lower GTN related to greater mean/maximal aIMT (regression coefficient = −0.004, $P = 0.004$; −0.005, $P = 0.005$) and greater mean/maximal cIMT (regression coefficient = −0.002, $P = 0.006$; −0.002, $P = 0.01$). Neither GTN nor FMD related to urinary albumin excretion.

Table 2—Multivariable models for aIMT in type 1 diabetes

	Mean aIMT		Maximal aIMT	
Predictor variable	Coefficient (SE)	*P*	Coefficient (SE)	*P*
Age	0.010 (0.004)	0.004	0.012 (0.005)	0.01
Diabetes duration	0.001 (0.002)	0.70	0.002 (0.002)	0.38
Waist circumference	0.001 (0.001)	0.41	0.001 (0.001)	0.28
Mean SBP	0.001 (0.001)	0.12	0.002 (0.001)	0.07
Mean DBP	−0.001 (0.001)	0.38	−0.001 (0.001)	0.71
LDL cholesterol	0.019 (0.008)	0.02	0.025 (0.011)	0.02
Urinary ACR	0.013 (0.006)	0.03	0.023 (0.007)	0.002
Center*		<0.0001		<0.0001

*Comparing all five centers simultaneously.

Table 3—Multivariable models for cIMT in type 1 diabetes

	Mean cIMT		Maximal cIMT	
Predictor variable	Coefficient (SE)	*P*	Coefficient (SE)	*P*
Sex (boys vs. girls)	0.023 (0.006)	0.0001	0.029 (0.007)	<0.0001
Diabetes duration	0.001 (0.001)	0.29	0.001 (0.001)	0.16
Waist circumference	0.001 (0.001)	0.29	0.001 (0.001)	0.37
Mean SBP	0.001 (0.001)	0.04	0.001 (0.001)	0.15
Mean DBP	−0.001 (0.001)	0.08	−0.001 (0.001)	0.23
HbA_{1c} (%)	−0.003 (0.002)	0.12	−0.003 (0.002)	0.29
Center*		<0.0001		<0.0001

*Comparing all five centers simultaneously.

CONCLUSIONS

We report the largest study of changes in two vascular beds in adolescents with type 1 diabetes. Structural changes in the aorta and carotid arteries could be detected in >50% of adolescents with type 1 diabetes, but there was a different related risk profile, and changes in the aorta were more common at this age. Aortic IMT was therefore able to better differentiate adolescents with type 1 diabetes from control subjects than was carotid wall changes. Aortic IMT enabled detection of the very early wall changes that are present with even small differences in urinary albumin excretion. This not only supports the concept of early intervention but provides a link between renal and cardiovascular disease.

The independent relationship between aIMT and urinary albumin excretion extends our knowledge of the pathogenesis of cardiovascular and renal disease in type 1 diabetes by showing that the first signs of the development of cardiovascular disease and diabetic nephropathy are related. The concept that microalbuminuria is a marker of a generalized endothelial damage, as well as a marker of renal disease, has been recognized for >20 years (3,20,21). Endothelial dysfunction is the first critical step in the development of atherosclerosis (22). Early rises in urinary albumin excretion precede the development of microalbuminuria and proteinuria (23). It follows that the first structural changes of atherosclerosis could relate to the first biochemical changes of diabetic nephropathy. To our knowledge, this is the first study to provide evidence of this.

We also provide more evidence that atherosclerosis begins in the abdominal aorta (14). More subjects had raised aIMT above the control mean, and aIMT, but not cIMT, was significantly greater in type 1 diabetic than in control subjects. This confirms our and others' smaller studies (15,16) suggesting that aIMT is a more sensitive measure in children and adolescents and therefore potentially a more sensitive outcome measure in intervention trials in this age-group. The difference in aIMT between type 1 diabetic patients and age- and sex-matched control subjects was equivalent to that seen with a 5- to 6-year age increase in the type 1 diabetic patients. aIMT was measurable in 92% of subjects, whereas cIMT was measurable in 100%. The association between the two was relatively weak, which is consistent with the possibility that they are increasing at different ages and driven by potentially different risk factors. The main technical difficulties that interfere with a satisfactory aIMT image are obesity and the extended study time by 15 min; these two factors are limitations to its use outside research studies with current ultrasound technology.

We have shown recently that adolescents enrolled in AdDIT with urinary albumin excretion rates in the upper tertile of the normal range, which predicts microalbuminuria in 85% of cases (6), have a small but significant increase in arterial stiffness (17). This Australian AdDIT cohort provides corroborative evidence for the early link between urinary albumin excretion and subclinical cardiovascular disease. The cross-sectional analysis prevents the unraveling of cause/effect relationships, and only longitudinal follow-up will clarify the temporal relationship between early nephropathy and early atherosclerosis.

The relationship between IMT and overweight may also have an impact on these longitudinal outcomes. The overweight epidemic has resulted in up to one-third of adolescents with type 1 diabetes in Australia being overweight or obese, consistent with international trends (24), and this could add to the cardiovascular burden of diabetes. BMI and waist circumference had direct relationships with IMT, but these did not remain on multivariate analysis of the cohort, 33% of whom were overweight or obese.

There was a significant center effect on the measurement of aIMT and cIMT. We chose to adjust for center differences in the multivariate models as opposed to standardizing the outcomes by center. However, a phantom image exchange had also been performed between the five centers, and this method of standardization did not significantly alter the multivariate analysis results. Importantly, there was no evidence for an effect modification by any center for the predictors (albumin excretion, LDL cholesterol, age, sex, and systolic blood pressure) of IMT.

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Table 4—IMT and vascular function in type 1 diabetic and control subjects

	Type 1 diabetic subjects	Control subjects	*P*
n	167	57	
Mean cIMT (mm)	0.43 ± 0.06	0.43 ± 0.06	0.81
Maximal cIMT (mm)	0.52 ± 0.07	0.51 ± 0.07	0.41
Mean aIMT (mm)	0.56 ± 0.11	0.51 ± 0.10	0.008
Maximal aIMT (mm)	0.67 ± 0.13	0.61 ± 0.12	0.005
FMD (%)	5.77 ± 4.3†	7.16 ± 4.48	0.001
GTN (%)	23.27 ± 7.51†	25.43 ± 8.61	0.001
Vessel diameter (cm)	0.28 ± 0.04†	0.27 ± 0.04	0.01

Data are means ± SD unless otherwise indicated. †*n* = 123.

study cohort, which recently investigated cIMT in type 1 diabetes, was of similar size, but subjects were older with longer duration of disease, as investigation was during later adolescence and early adulthood, and of mixed ethnic origins (13). aIMT was not measured and urinary albumin excretion was not included in their analysis. Our study demonstrates that atherosclerosis can be detected by early adolescence after a shorter duration of disease. In SEARCH CVD, only HbA_{1c} independently related to cIMT (13). As in SEARCH CVD, the majority of our type 1 diabetic subjects (78%) did not achieve target metabolic control of HbA_{1c} <7.5% (<58 mmol/mol), consistent with a recent audit of Australian pediatric diabetes clinics (25), representing >80% of children with type 1 diabetes in Australia, including the five centers participating in this study. Metabolic control is an established risk factor of cIMT in type 1 diabetes (26), but at this early stage of atherosclerosis, we emphasize the additional importance of other cardiovascular risk factors.

The study is not without its limitations. The relatively small number of control subjects provided comparative data for IMT and vascular function only, as measured on the same machine by the same sonographer. However, our primary purpose was to examine the relationship between IMT and risk factors in type 1 diabetes. We would require very large numbers of control subjects to examine a relationship between ACR and IMT in the normal childhood population.

In conclusion, atherosclerosis is detectable from early adolescence in type 1 diabetes. Its early independent associations are male sex, age, systolic blood pressure, LDL cholesterol, and, importantly, urinary albumin excretion. Changes appear to occur first in the aorta in type 1 diabetes, as has been detected in normal childhood. Early rises in urinary albumin excretion during adolescence not only are important for determining risk of progression to microalbuminuria and diabetic nephropathy but also may alert the clinician to increased risk of cardiovascular disease. Their detection during adolescence should prompt extra attention to modifiable cardiovascular risk factors in addition to efforts to maximize metabolic control.

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Author Contributions. O.M. acquired data, analyzed and interpreted data, and critically revised the manuscript. A.S.P. developed the study concept and design, acquired data, critically revised the manuscript, and supervised the study. T.S. analyzed and interpreted data, critically revised the manuscript, and performed statistical analysis. T.W.J., K.C.D., and E.D. developed the study concept and design, acquired data, critically revised the manuscript, and obtained funding. F.J.C. acquired data and obtained funding. A.C. and M.E.C. acquired data, critically revised the manuscript, and obtained funding. R.G. acquired data and supervised the study. N.D. developed the study concept and design and analyzed and interpreted data. D.Da. developed the study concept and design. D.Du. developed the study concept and design, critically revised the manuscript, and obtained funding. J.D. developed the study concept and design and critically revised the manuscript. J.J.C. contributed to the study concept and design, acquired data, critically revised the manuscript, analyzed and interpreted data, obtained funding, and supervised the study. O.M., T.S., and J.J.C. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Kavey RE, Allada V, Daniels SR, et al.; American Heart Association Expert Panel on Population and Prevention Science; American Heart Association Council on Cardiovascular Disease in the Young; American Heart Association Council on Epidemiology and Prevention; American Heart Association Council on Nutrition, Physical Activity and Metabolism; American Heart Association Council on High Blood Pressure Research; American Heart Association Council on Cardiovascular Nursing; American Heart Association Council on the Kidney in Heart Disease; Interdisciplinary Working Group on Quality of Care and Outcomes Research. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. Circulation 2006;114:2710–2738

2. Jørgensen ME, Almdal TP, Carstensen B. Time trends in mortality rates in type 1 diabetes from 2002 to 2011. Diabetologia 2013;56:2401–2404

3. Deckert T, Feldt-Rasmussen B, Borch-Johnsen K, Jensen T, Kofoed-Enevoldsen A. Albuminuria reflects widespread vascular damage. The Steno hypothesis. Diabetologia 1989;32:219–226

4. Krantz JS, Mack WJ, Hodis HN, Liu CR, Liu CH, Kaufman FR. Early onset of subclinical atherosclerosis in young persons with type 1 diabetes. J Pediatr 2004;145:452–457

5. Marcovecchio ML, Tossavainen PH, Dunger DB. Status and rationale of renoprotection studies in adolescents with type 1 diabetes. Pediatr Diabetes 2009;10:347–355

6. Dunger DB, Schwarze CP, Cooper JD, et al. Can we identify adolescents at high risk for nephropathy before the development of microalbuminuria? Diabet Med 2007;24:131–136

7. Molitch ME, Steffes M, Sun W, et al.; Epidemiology of Diabetes Interventions and Complications Study Group. Development and progression of renal insufficiency with and without albuminuria in adults with type 1 diabetes in the Diabetes Control and Complications Trial and the Epidemiology of Diabetes Interventions and Complications study. Diabetes Care 2010;33:1536–1543

8. Krolewski AS, Niewczas MA, Skupien J, et al. Early progressive renal decline precedes the onset of microalbuminuria and its progression to macroalbuminuria. Diabetes Care 2014;37:226–234

9. de Boer IH; DCCT/EDIC Research Group. Kidney disease and related findings in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study. Diabetes Care 2014;37:24–30

10. Adolescent type 1 Diabetes cardio-renal Intervention Trial Research Group. Adolescent type 1 Diabetes Cardio-renal Intervention Trial (AdDIT). BMC Pediatr 2009;9:79

11. Amato M, Montorsi P, Ravani A, et al. Carotid intima-media thickness by B-mode ultrasound as surrogate of coronary atherosclerosis: correlation with quantitative coronary angiography and coronary intravascular ultrasound findings. Eur Heart J 2007;28:2094–2101

12. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. Circulation 2007;115:459–467

13. Urbina EM, Dabelea D, D'Agostino RB Jr, et al. Effect of type 1 diabetes on carotid structure and function in adolescents and young adults: the SEARCH CVD study. Diabetes Care 2013;36:2597–2599
14. McGill HC Jr, McMahan CA, Herderick EE, Malcom GT, Tracy RE, Strong JP. Origin of atherosclerosis in childhood and adolescence. Am J Clin Nutr 2000;72(Suppl):1307S–1315S
15. Järvisalo MJ, Jartti L, Näntö-Salonen K, et al. Increased aortic intima-media thickness: a marker of preclinical atherosclerosis in high-risk children. Circulation 2001;104:2943–2947
16. Harrington J, Peña AS, Gent R, Hirte C, Couper J. Aortic intima media thickness is an early marker of atherosclerosis in children with type 1 diabetes mellitus. J Pediatr 2010;156:237–241
17. Marcovecchio ML, Woodside J, Jones T, et al.; AdDIT Investigators. Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial (AdDIT): urinary screening and baseline biochemical and cardiovascular assessments. Diabetes Care 2014;37:805–813
18. Wiltshire EJ, Gent R, Hirte C, Pena A, Thomas DW, Couper JJ. Endothelial dysfunction relates to folate status in children and adolescents with type 1 diabetes. Diabetes 2002;51:2282–2286
19. Ogden CL, Kuczmarski RJ, Flegal KM, et al. Centers for Disease Control and Prevention 2000 growth charts for the United States: improvements to the 1977 National Center for Health Statistics version. Pediatrics 2002;109:45–60
20. Viberti GC, Hill RD, Jarrett RJ, Argyropoulos A, Mahmud U, Keen H. Microalbuminuria as a predictor of clinical nephropathy in insulin-dependent diabetes mellitus. Lancet 1982;1:1430–1432
21. Rossing P, Hougaard P, Borch-Johnsen K, Parving HH. Predictors of mortality in insulin dependent diabetes: 10 year observational follow up study. BMJ 1996;313:779–784
22. Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s. Nature 1993;362:801–809
23. Schultz CJ, Neil HA, Dalton RN, Dunger DB; Oxforn Regional Prospective Study Group. Risk of nephropathy can be detected before the onset of microalbuminuria during the early years after diagnosis of type 1 diabetes. Diabetes Care 2000;23:1811–1815
24. MacKenzie KE, Wiltshire EJ, Gent R, Hirte C, Piotto L, Couper JJ. Folate and vitamin B6 rapidly normalize endothelial dysfunction in children with type 1 diabetes mellitus. Pediatrics 2006;118:242–253
25. Cameron F, Cotterill A, Couper J, et al. Short report: Care for children and adolescents with diabetes in Australia and New Zealand: have we achieved the defined goals? J Paediatr Child Health 2013;49:E258–E262
26. Nathan DM, Lachin J, Cleary P, et al.; Diabetes Control and Complications Trial; Epidemiology of Diabetes Interventions and Complications Research Group. Intensive diabetes therapy and carotid intima-media thickness in type 1 diabetes mellitus. N Engl J Med 2003;348:2294–2303