Renal and Cardiovascular Risk According to Tertiles of Urinary Albumin-to-Creatinine Ratio: The Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial (AdDIT)

*M. Loredana Marcovecchio,[1] Scott T. Chiesa,[2] Jane Armitage,[3] Denis Daneman,[4] Kim C. Donaghue,[5] Timothy W. Jones,[6] Farid H. Mahmud,[4] Sally M. Marshall,[7] H. Andrew W. Neil,[8] R. Neil Dalton,[9] John Deanfield,[2] and David B. Dunger,[1,10] on behalf of the Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial (AdDIT) Study Group**

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OBJECTIVE

Baseline data from the Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial (AdDIT) indicated that tertiles of urinary albumin-to-creatinine ratios (ACRs) in the normal range at age 10–16 years are associated with risk markers for diabetic nephropathy (DN) and cardiovascular disease (CVD). We aimed to determine whether the top ACR tertile remained associated with DN and CVD risk over the 2–4-year AdDIT study.

RESEARCH DESIGN AND METHODS

One hundred fifty adolescents (mean age 14.1 years [SD 1.6]) with baseline ACR in the upper tertile (high-ACR group) recruited to the AdDIT trial, who remained untreated, and 396 (age 14.3 years [1.6]) with ACR in the middle and lower tertiles (low-ACR group), who completed the parallel AdDIT observational study, were evaluated prospectively with assessments of ACR and renal and CVD markers, combined with carotid intima-media thickness (cIMT) at baseline and end of study.

RESULTS

After a median follow-up of 3.9 years, the cumulative incidence of microalbuminuria was 16.3% in the high-ACR versus 5.5% in the low-ACR group (log-rank $P < 0.001$). Cox models showed independent contributions of the high-ACR group (hazard ratio 4.29 [95% CI 2.08–8.85]) and HbA_{1c} (1.37 [1.10–1.72]) to microalbuminuria risk. cIMT change from baseline was significantly greater in the high- versus low-ACR group (mean difference 0.010 mm [0.079], $P = 0.006$). Changes in estimated glomerular filtration rate, systolic blood pressure, and hs-CRP were also significantly greater in the high-ACR group ($P < 0.05$).

CONCLUSIONS

ACR at the higher end of the normal range at the age of 10–16 years is associated with an increased risk of progression to microalbuminuria and future CVD risk, independently of HbA_{1c}.

[1]*Department of Paediatrics, University of Cambridge, Cambridge, U.K.*
[2]*National Centre for Cardiovascular Prevention and Outcomes, University College London, London, U.K.*
[3]*Medical Research Council Population Health Research Unit, Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford, Oxford, U.K.*
[4]*Department of Paediatrics, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada*
[5]*Institute of Endocrinology and Diabetes, The Children's Hospital at Westmead, University of Sydney, Camperdown, New South Wales, Australia*
[6]*Telethon Kids Institute, University of Western Australia, Perth, Western Australia, Australia*
[7]*Institute of Cellular Medicine (Diabetes), Faculty of Clinical Medical Sciences, Newcastle University, Newcastle upon Tyne, U.K.*
[8]*Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, U.K.*
[9]*Guy's and St Thomas' National Health Service Foundation Trust, London, U.K.*
[10]*Wellcome Trust-MRC Institute of Metabolic Science, University of Cambridge, Cambridge, U.K.*

Corresponding author: David B. Dunger, dbd25@cam.ac.uk.

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**A complete list of the members of the AdDIT Study Group can be found in the Supplementary Data online.*

The prognosis of young people with type 1 diabetes remains poor. Recent data indicate that for a 20-year-old person with type 1 diabetes, life expectancy is reduced by 10–13 years compared with the respective background population (1,2). Diabetic nephropathy (DN) and cardiovascular disease (CVD) are the main contributors to morbidity and mortality, and diabetic retinopathy is a major cause of vision loss (3).

Microalbuminuria has been recognized for a long time as a hallmark of DN and a predictor of CVD in people with type 1 diabetes (4,5). However, recent evidence indicates that increases in urinary albumin excretion even within the normal range, and thus below the specific cutoff for the definition of microalbuminuria, may predict renal and cardiovascular risk in adults with diabetes as well as in the general population (6–8).

In young people with type 1 diabetes, early increases in urinary albumin excretion during the first years after diagnosis are predictive of future risk of DN (9). In longitudinal cohorts of adolescents with type 1 diabetes, tertiles of urinary albumin-to-creatinine ratio (ACR) adjusted for age, diabetes duration, and sex, at the age of 11–16 years, were highly predictive of those individuals who went on to develop microalbuminuria and macroalbuminuria after puberty (10).

The Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial (AdDIT) was primarily designed to explore the potential cardio-renal protection provided by ACE inhibitors and statins in adolescents with type 1 diabetes at increased risk of vascular complications based on an ACR in the upper tertile of the normal range (11,12). The study protocol also included a group of adolescents with an ACR in the lower and middle tertiles who participated in a parallel observational study (11).

At baseline, AdDIT participants with an ACR in the upper tertile showed evidence of glomerular hyperfiltration, increased lipid levels and pulse wave velocity, and impaired autonomic function (11,13,14), despite similar HbA_{1c} values across ACR tertiles. These data supported the hypothesis that risk stratification using ACR tertiles during early adolescence may be helpful for the early identification of patients at risk for developing vascular complications.

We have now evaluated whether early stratification based on tertiles of ACR in adolescents aged 10–16 years participating in the AdDIT study could predict those at higher risk of developing renal and cardiovascular complications during a 2–4-year follow-up period.

RESEARCH DESIGN AND METHODS

Study Design and Participants

The study population consisted of adolescents with type 1 diabetes screened and recruited into the AdDIT Trial and the parallel observational study (11). The screened population of 4,407 adolescents (age between 10 and 16 years) with type 1 diabetes from the U.K., Canada, and Australia provided two sets of three consecutive early morning urine samples for the assessment of urinary ACR. The three ACR measures at each visit were averaged on the log ACR scale, and the subject's average residual was calculated using an algorithm derived from previous longitudinal studies of the natural history of microalbuminuria (10). This algorithm allowed adjustments for age, sex, and type 1 diabetes duration. If the residual was above log 1.2, the participant was assigned to the upper tertile of ACR. Values between 0.8 and 1.2 identified the middle ACR tertile, whereas values <0.8 identified the lower ACR tertile. The upper tertile of ACR was used to classify adolescents at higher risk for vascular complications (based on previous findings [10]) who were eligible for the AdDIT trial (trial cohort), whereas the lower and middle tertiles identified adolescents with a lower risk who were eligible for the observational arm of the AdDIT study (11). Further details of the inclusion and exclusion criteria were previously reported (11,12).

Between 2009 and 2013, 443 adolescents (10–16 years) with ACR in the upper tertile of the normal range were randomized to an ACE inhibitor (quinapril) or matching placebo and separately to a statin (atorvastatin) or matching placebo in a 2×2 factorial design over a 2–4-year treatment period until March 2016 (12). For the present analysis, only data collected from adolescents randomized to the placebo ACE inhibitor and placebo statin were used ($n = 109$). These 109 adolescents and an additional 41 adolescents with baseline ACR in the upper tertile screened for AdDIT, who declined to take part in the trial but agreed to be followed up, represent the "high-ACR group" ($n = 150$). Screened adolescents with an ACR in the middle or lower tertile ($n = 404$) were recruited to the parallel AdDIT observational study. Eight of them withdrew from the study before the baseline visit, and the remaining 396 represent the "low-ACR group" (Supplementary Fig. 1). Both groups underwent similar baseline and follow-up assessments, according to a standardized protocol (11).

The study sponsor was the University of Cambridge and Cambridge University Hospitals National Health Service Foundation Trust. The study protocol conformed to the Declaration of Helsinki and was approved by the Cambridge University Hospitals and participating research ethics committees. Parents of participants provided written informed consent, and study participants were asked to provide their assent, until they reached an age when they could consent to study follow-up.

Procedures

Baseline Assessment

Baseline visits for the high- and low-ACR groups included measurement of height, weight, waist circumference, and arterial blood pressure. Nonfasting blood samples were collected for local HbA_{1c} measurements and central assessments of CVD and renal markers. These included a lipid profile (total cholesterol, triglycerides, HDL cholesterol, and LDL cholesterol), other CVD markers (hs-CRP and asymmetric dimethylarginine [ADMA]), and renal markers (creatinine and cystatin C). All study participants also attended one of the designated centers for standardized carotid intima-media thickness (cIMT) assessment.

Follow-up Visits

Every 6 months, three early morning urines were collected for central assessment of ACR; height, weight, waist circumference, pubertal stage, blood pressure, and smoking status were recorded; and blood samples were taken for local HbA_{1c}. Annual blood samples were collected for centralized measurements of renal and CVD markers as at baseline.

Throughout the trial, treating physicians were encouraged to strive for optimal glycemic control, but targets and methods of insulin delivery were not stipulated in the protocol.

Biochemistry

HbA_{1c} was assessed locally, using Diabetes Control and Complications Trial (DCCT)–aligned methods, whereas all other biochemical measurements were performed in a central laboratory (WellChild Laboratory, Evelina London Children's Hospital, U.K.), using standardized methods.

Urine albumin was measured using nephelometric immunoassay according to the manufacturer's instructions (BN Prospec; Siemens). Urine albumin concentrations below the limit of quantitation of nephelometry, typically <2.1 mg/L, were measured using ELISA. Between-batch imprecision 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 (MSMS) 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 MSMS. Between-batch imprecision (n = 30) was 2.8% at 66.1 μmol/L and 2.5% at 333.3 μmol/L. Cystatin C was measured by particle-enhanced nephelometric immunoassay according to the manufacturer's instructions (BN Prospec). Between-batch imprecision (n = 38) for cystatin C was 3.5% at 0.87 mg/L and 3.6% at 4.64 mg/L. Plasma ADMA was measured using a chromatographic stable isotope dilution fragmentation-specific electrospray MSMS. Between-batch imprecision (n = 30) for ADMA was 2.5% at 401 nmol/L, 2.7% at 917 nmol/L, and 2.7% at 2,413 nmol/L. hs-CRP was measured by particle-enhanced nephelometric immunoassay according to the manufacturer's instructions (BN Prospec). Between-batch imprecision (n = 38) was 5.8% at 0.89 mg/L and 3.6% at 4.73 mg/L. Total cholesterol (second-generation formulation), HDL cholesterol (third-generation formulation), LDL cholesterol, and triglycerides were measured colorimetrically on a COBAS INTEGRA 400 plus according to the manufacturer's instructions. Between-batch imprecision for total cholesterol (n = 35) was 2.6% at 4.71 mmol/L and 2.1% at 8.62 mmol/L, for HDL cholesterol (n = 35) was 3.1% at 0.86 mmol/L and 3.9% at 1.49 mmol/L, for LDL cholesterol (n = 36) was 3.1% at 3.07 mmol/L and 2.5% at 4.92 mmol/L, and for triglycerides (n = 35) was 2.9% at 1.47 mmol/L and 2.8% at 4.82 mmol/L.

Vascular Assessments

Ultrasound scanning for cIMT was performed at 11 specialist vascular centers at baseline and at the end of follow-up. Vascular sonographers were accredited before the study commenced. Sonographer training was conducted through the Vascular Physiology Unit at University College London, which has extensive experience in undertaking large-scale vascular phenotyping trials in children, and included a 1-week intensive training course in London for all study sonographers. Sonographers were accredited before the study commenced, and intrasonographer reproducibility on five subjects scanned at least 1 week apart was <5%. A single reader analyzed all cIMT scans in the core laboratory. Intrareader reproducibility on 50 randomly selected study scans was 2.1%.

Common carotid artery ultrasound images were acquired using a standardized protocol. The artery was scanned in the ear-ear plain with the head rotated to 45° from the midpoint. Images triggered on the R wave of the electrocardiogram were recorded in DICOM format as cine loop files for offline analysis (Carotid Analyzer; Medical Imaging Applications, Coralville, IA). The cIMT value was taken as the average of three end-diastolic measurements. cIMT measurements were made on a single segment of arterial wall 5–10 mm in length, at least 10 mm proximal to the bifurcation.

Calculations

Estimated glomerular filtration rate (eGFR) was calculated from plasma creatinine with a modified Schwartz formula, based on our previous study in adolescents with type 1 diabetes, eGFR (mL/min/1.73 m^2) = 42 × height (cm)/plasma creatinine (μmol/L) (15,16), and the Zappitelli equation (age <18 years), $43.82 \times (1/\text{cystatin C})^{0.635} \times (1/\text{creatinine})^{0.547} \times 1.35^{\text{height}}$ (17).

Study Outcome Measures

The primary outcome measure was incidence of microalbuminuria in relation to baseline ACR tertiles. Microalbuminuria was defined as an ACR >3.5 mg/mmol (in males) or 4 mg/mmol (in females) in at least two out of three early morning urines at any study visit. Case subjects with microalbuminuria at screening were excluded from this analysis. Time to first incidence of microalbuminuria was analyzed as a time-to-event variable using the calendar date when microalbuminuria was observed or censoring at the final visit if microalbuminuria was never observed.

Secondary outcome measures included changes in cIMT between baseline and the end of study, trends in cardiovascular risk factors during the study period (blood pressure, lipid levels, hs-CRP, and ADMA), trends in renal markers (eGFR), and trends in glycemic control as measured by HbA_{1c}.

Statistical Analysis

Data are summarized as mean ± SD or median (interquartile range) unless otherwise specified. Nonnormally distributed variables were log transformed before analysis. Between-group baseline comparisons were performed by unpaired Student t tests for continuous variables and by χ^2 or Fisher exact test for categorical variables.

For the primary end point, the assessment of the effect of the baseline ACR group (low vs. high) was performed by Kaplan-Meier estimation of survival curves (and compared by log-rank test) and by Cox proportional hazards models, and results are expressed as hazard ratios (HRs). The univariate association between baseline and longitudinal clinical and laboratory parameters (ACR category, HbA_{1c}, age, age at diagnosis, duration, blood pressure, lipids, and eGFR) and microalbuminuria was assessed in univariate Cox regression models. Variables with $P < 0.05$ were then included in a multivariate model.

For the analysis of cIMT, assessed only at baseline and follow-up, an ANCOVA model was used to estimate the effect of ACR categories (low- vs. high-ACR group). The final cIMT measurement was used as the dependent variable in the model, and adjustments were made for baseline cIMT, age, sex, HbA_{1c}, blood pressure, and cholesterol.

Linear mixed models, adjusted for age and sex, were used to assess differences over time in the high- versus low-ACR group in the secondary continuous end points assessed at multiple time points during the study period.

We considered $P < 0.05$ as significant for the primary outcome. For secondary and exploratory outcomes, *P* values are not adjusted but should be interpreted cautiously.

RESULTS

Cohort Description

The study population consisted of all participants completing the observational arm of the AdDIT study (low-ACR group, *n* = 396) and the 150 with ACR in the upper tertile unexposed to the active trial drugs (high-ACR group) for a total of 546 participants (Supplementary Fig. 1). The duration of follow-up was similar in the low- and high-ACR groups: 3.9 years (3.3–4.1) vs. 3.9 years (3.1–4.1).

Baseline Characteristics

The general characteristics of the study participants at baseline are shown in Table 1. Adolescents in the high-ACR group were slightly older at the time of diabetes diagnosis and had shorter diabetes duration than those in the low-ACR group. There was a similar sex distribution and no differences in anthropometric parameters (height, weight, BMI, and waist circumference) between the two groups. Biochemical data showed similar HbA_{1c} values between the two groups, whereas ACR levels were, by definition, higher in the high-ACR group (Table 1). No significant differences were found in cholesterol and triglyceride levels, ADMA, and hs-CRP, whereas creatinine levels were lower in the high-ACR group, and this was associated with a higher eGFR (Table 1).

Table 1—Baseline characteristics of the study population

	Low-ACR group	High-ACR group	*P*
n	396	150	
Sex, male, *n* (%)	211 (53.3)	77 (51.3)	0.95
Age (years)	14.3 (1.6)	14.1 (1.6)	0.17
Age at diagnosis (years)	6.9 (3.6)	8.2 (3.1)	0.001
Duration of diabetes (years)	7.3 (3.4)	5.9 (3.1)	<0.001
Height (cm)	163.5 (10.6)	162.1 (10.1)	0.17
Weight (kg)	59.0 (13.9)	57.1 (12.9)	0.15
Waist circumference (cm)	72.5 (16.0)	73.6 (9.0)	0.41
BMI (kg/m^2)	21.9 (3.8)	21.6 (3.6)	0.38
Systolic blood pressure (mmHg)	115.6 (11.3)	116.4 (13.3)	0.52
Diastolic blood pressure (mmHg)	67.1 (7.7)	65.6 (7.8)	0.05
HbA_{1c} (%)	8.4 (1.3)	8.5 (1.3)	0.72
HbA_{1c} (mmol/mol)	68.8 (14.2)	69.3 (14.6)	0.72
Total cholesterol (mmol/L)	4.36 (0.84)	4.28 (0.90)	0.38
HDL cholesterol (mmol/L)	1.57 (0.42)	1.55 (0.36)	0.71
LDL cholesterol (mmol/L)	2.31 (0.66)	2.28 (0.66)	0.62
Triglycerides (mmol/L)	0.83 (0.64–1.19)	0.88 (0.62–1.20)	0.72
hs-CRP (mg/L)	0.49 (0.19–1.14)	0.59 (0.19–1.20)	0.21
ADMA (nmol/L)	471.2 (74.7)	483.7 (93.2)	0.16
ACR (mg/mmol)	0.63 (0.53–0.74)	1.23 (0.99–1.83)	<0.001
Cystatin C (mg/L)	0.86 (0.13)	0.84 (0.13)	0.22
Creatinine (μmol/L)	55.1 (11.1)	52.0 (10.0)	0.009
eGFR (Schwartz) (mL/min/1.73 m^2)	128.5 (21.2)	135.2 (24.6)	0.007
eGFR (Zappitelli) (mL/min/1.73 m^2)	104.9 (16.2)	109.2 (17.5)	0.02
cIMT (mm)	0.440 (0.041)	0.444 (0.051)	0.38

Data are mean (SD) or median (interquartile range) unless otherwise specified.

Incidence of Microalbuminuria

At baseline, 10 of the 546 (1.8%) participants had ACR in the microalbuminuria range, all in the high-ACR group. These study participants were excluded from the analysis of incident cases of microalbuminuria.

During the median follow-up of 3.9 years, 31 study participants developed microalbuminuria. The cumulative incidence of microalbuminuria was significantly higher in the high- than in the low-ACR group (16.3% vs. 5.5%, log-rank $P < 0.001$) (Fig. 1).

The univariate associations between baseline clinical and laboratory parameters (ACR group, HbA_{1c}, age, age at diagnosis, duration, LDL cholesterol, blood pressure, and eGFR) and microalbuminuria were assessed in univariate Cox regression models (Table 2). Variables with $P < 0.05$ (ACR group and HbA_{1c}) were then included in a multivariate model, which showed that the ACR group (low vs. high: HR 4.29 [95% CI 2.08–8.85]) and HbA_{1c} (1.37 [1.10–1.72]) were independent factors associated with future risk of microalbuminuria (Table 2).

Similar results were obtained when postbaseline mean values of predictors

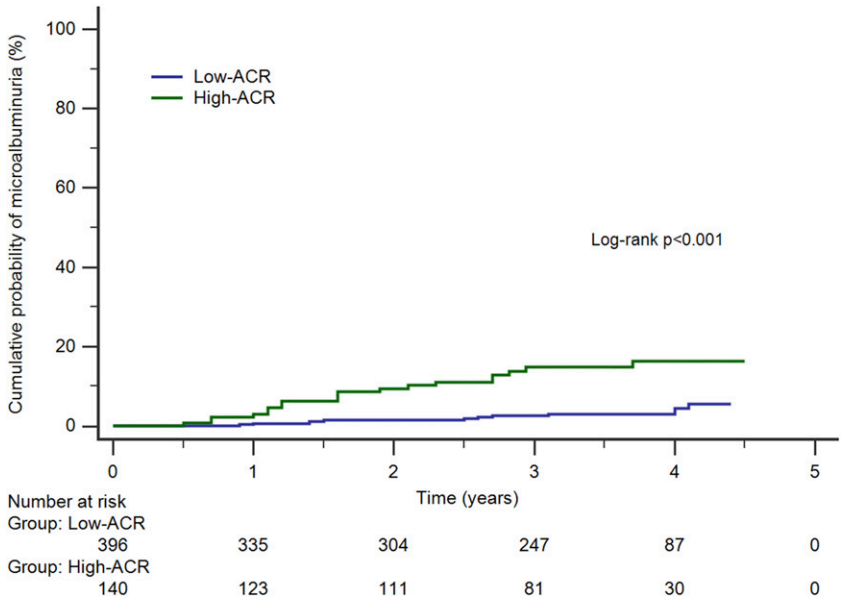

Figure 1—Cumulative incidence of microalbuminuria in the low- and high-ACR groups. Time is calculated from the beginning of the study.

Table 2—Cox regression models for incident microalbuminuria

	HR	95% CI	*P* value
Univariate models			
ACR group (low vs. high)	4.52	2.20–9.33	<0.001
HbA_{1c} (per %)	1.39	1.11–1.73	0.003
Sex (female vs. male)	0.61	0.30–1.25	0.18
Age at diagnosis (per year)	0.98	0.88–1.08	0.64
Duration at baseline (per year)	0.99	0.71–1.13	0.87
Age at baseline (per year)	0.89	0.71–1.13	0.35
Systolic blood pressure (per mmHg)	0.99	0.97–1.03	0.73
Diastolic blood pressure (per mmHg)	0.99	0.95–1.04	0.99
LDL cholesterol (mmol/L)	0.75	0.41–1.37	0.35
eGFR (per mL/min/1.73 m^2)	1.00	0.98–1.03	0.81
Multivariate model			
ACR group (low vs. high)	4.29	2.08–8.85	<0.001
HbA_{1c} (per %)	1.37	1.10–1.72	0.006

were included in the Cox regression models (Supplementary Table 1).

The independent effect of HbA_{1c} and baseline ACR on the cumulative incidence of microalbuminuria during follow-up was further explored by dividing the study population into tertiles of mean HbA_{1c}. This analysis showed a progressive increase in microalbuminuria from the lower to the upper tertile of HbA_{1c} both in the low- and high-ACR groups (Supplementary Fig. 2).

cIMT

cIMT was assessed at baseline in 149 adolescents from the high-ACR group and 370 from the low-ACR group. cIMT was then reassessed at the final visit in 126 high- and 266 low-ACR participants. At baseline, mean cIMT values were comparable between the high- and low-ACR groups (0.444 mm [0.051] vs. 0.440 mm [0.041], *P* = 0.38) (Fig. 2). In contrast, at the end of the follow-up period, cIMT was significantly higher in the high- than in the low-ACR group (0.448 mm [0.050] vs. 0.434 mm [0.043], *P* = 0.009).

The change in cIMT from baseline differed significantly between the high- and low-ACR groups (mean difference 0.010 [SD 0.079], *P* = 0.006), and this remained significant even after adjusting for age, sex, blood pressure, HbA_{1c}, and LDL cholesterol (*P* = 0.008). Similar results were obtained when mean levels of HbA_{1c}, blood pressure, and LDL cholesterol during the study period were included in the ANCOVA model for the adjustments instead of baseline values (*P* = 0.014).

Other Secondary Outcomes

Linear mixed models were used to assess changes over time in the other key renal and cardiovascular markers assessed in the two study groups (Table 3).

No significant differences were found in HbA_{1c}, which showed a small increase in both groups. Similarly, there were no significant differences in lipid levels. Significant differences were found in eGFR (assessed by both the Schwartz and Zappitelli formulas), which were greater over time in the high- versus low-ACR group (mean difference 4.84 [SE 1.49], *P* = 0.01), reflecting greater rates of hyperfiltration, as well as in systolic blood pressure (2.08 [1.00], *P* = 0.03) and hs-CRP (0.85 [0.32], *P* = 0.01) (Table 3).

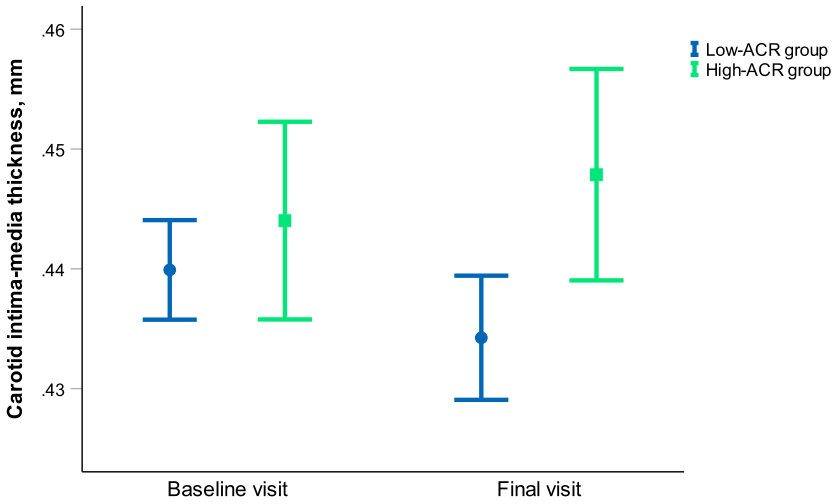

Figure 2—Comparison of cIMT at baseline and follow-up between the high- and low-ACR groups. Data are means and 95% CI. Baseline: *P* = 0.38; final: *P* = 0.009.

CONCLUSIONS

This study showed that in a cohort of ~546 adolescents with type 1 diabetes, assessed at the age of 10–16 years, a higher ACR even within the normal range was associated with a greater risk of progression to microalbuminuria, a higher eGFR, and a worse cardiovascular profile, as indicated by a thicker cIMT and greater blood pressure and hs-CRP values during a 2–4-year follow-up period.

Variation in urinary albumin excretion has long been adopted as a screening tool for the detection of DN, where levels in the microalbuminuric range are indicative of incipient nephropathy and risk of progression to macroalbuminuria and end-stage renal disease (5,18). However, the predictive value of these observations has been partly put in doubt by the high rates of reversal from microalbuminuria to normoalbuminuria over subsequent years (19) and the observation that some individuals may show decline in GFR in the absence of microalbuminuria (20). Nevertheless, the links between early evidence of DN, including microalbuminuria, and CVD risk in type 1 diabetes remain robust (21,22).

In the normal population, associations between variations in ACR within the normal range and future CVD risk have been observed (8,23), perhaps suggesting that increases in albumin excretion may be a continuous marker for both CVD and DN risk in individuals with type 1 diabetes.

During the screening phase of the AdDIT study, we observed that young people (10–16 years) with an ACR in the highest tertile, although still within the normal range, already showed evidence of increased risk for CVD, as indicated by

Table 3—Mean changes over time in cardiovascular and renal markers: high- vs. low-ACR group

	β-Estimate (SE)	*P*
Total cholesterol (mmol/L)	−0.11 (0.08)	0.20
HDL cholesterol (mmol/L)	−0.05 (0.03)	0.11
LDL cholesterol (mmol/L)	−0.07 (0.07)	0.29
Triglycerides (mmol/L)	0.10 (0.06)	0.09
ADMA (nmol/L)	2.07 (5.80)	0.72
hs-CRP (mg/L)	0.85 (0.32)	0.01
Systolic blood pressure (mmHg)	2.08 (1.00)	0.03
Diastolic blood pressure (mmHg)	−0.06 (0.58)	0.92
eGFR (Zappitelli) (mL/min/1.73 m^2)	4.84 (1.49)	0.01
eGFR (Schwartz) (mL/min/1.73 m^2)	5.90 (1.71)	0.01
HbA_{1c} (%)	0.08 (0.14)	0.54

Results are from linear mixed models, adjusted for age and sex. Data are reported as β-estimate and SE. β-Estimates are equal to the mean difference between the high- and low-ACR groups.

greater arterial stiffness and signs of impaired cardiac autonomic function, as well as higher rates of glomerular hyperfiltration, compared with adolescents in the lower/middle tertiles of ACR (11,13,14). The current longitudinal data from the AdDIT high- and low-ACR groups support these initial observations.

The rate of progression to microalbuminuria was much greater in participants in the higher than in the lower and middle tertiles of ACR at baseline. As expected, HbA_{1c} was also an independent risk factor for the development of microalbuminuria in both the low- and high-ACR groups.

Of interest, the higher eGFR levels associated with ACR in the upper tertile at baseline persisted during the follow-up period, although baseline eGFR was not an independent predictor of incident microalbuminuria. However, the persistence of glomerular hyperfiltration during the study period could be an additional risk factor for progression toward more advanced stages of DN and long-term development of CVD (24,25).

The higher rates of microalbuminuria in the high-ACR group may not necessarily predict future risk of DN, as in adolescent cohorts we have observed high rates of reversal at the end of puberty, particularly in those with good glycemic control (26), but both intermittent and persistent microalbuminuria did predict all future cases of macroalbuminuria (26). This is also in line with recent data from the DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC) study, highlighting the predictive role of even intermittent microalbuminuria for future renal and CVD outcomes (22).

The cardiovascular outcomes in the high- and low-ACR groups also supported the baseline observations. The measured cardiovascular surrogate outcome cIMT demonstrated worsening over time in the high-ACR group. This was supported by longitudinal changes in hs-CRP and systolic blood pressure, perhaps reflecting increased CVD risk in those with the highest ACR. hs-CRP is a well-known cardiovascular risk marker (27), and we previously found that its levels tend to increase in parallel with the development of microalbuminuria (28). Although hs-CRP increased in the whole study population, its levels were consistently higher in the high-ACR group. Similarly, although there were no differences at baseline in blood pressure, over time, levels of systolic blood pressure were higher in the high-ACR group. Higher levels of cardiovascular risk factors, such as blood pressure and inflammatory markers, throughout adolescence could contribute to the lifetime risk of CVD, which still remains the leading cause of morbidity and mortality among individuals with type 1 diabetes (29).

Thus, AdDIT provides evidence that variations in albumin excretion in individuals with type 1 diabetes as young as 10–16 years old may partially predict future DN and CVD risk, but the extent to which this adds to prediction based on HbA_{1c} and other risk factors still needs to be determined. The large sample size of the study cohort and the well-standardized methods for collection and analysis of clinical, biochemical, and vascular data support the validity of the study findings. However, the present findings were derived from a very selective study population recruited into a clinical trial and parallel observational study. Indeed, there is a need for replication and validation of the study findings in other cohorts of adolescents and older subjects with type 1 diabetes. There also remains a need to assess the value of the ACR tertiles in predicting long-term complications during early adulthood. Over the next 3–4 years, AdDIT participants will be entering the second/third decade of type 1 diabetes and that critical postpubertal period when the first direct evidence of vascular complications is observed (30). Thus, ongoing follow-up of the cohort could help in answering this relevant question.

In conclusion, these data support the concept that risk stratification using ACR during early adolescence may be valuable for the early identification of patients at risk for developing renal and cardiovascular complications and to guide the implementation of preventive and treatment strategies to reduce the burden associated with vascular complications of diabetes.

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