Cardiac Autonomic Dysfunction Is Associated With High-Risk Albumin-to-Creatinine Ratio in Young Adolescents With Type 1 Diabetes in AdDIT (Adolescent Type 1 Diabetes Cardio-Renal Interventional Trial)

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OBJECTIVE

This study examined the association between cardiac autonomic dysfunction and high albumin-to-creatinine ratio (ACR) in adolescents with type 1 diabetes.

RESEARCH DESIGN AND METHODS

Adolescents recruited as part of a multicenter screening study (*n* = 445, 49% female, aged 10–17 years, mean duration 6.9 years; mean HbA_{1c} 8.4%, 68 mmol/mol) underwent a 10-min continuous electrocardiogram recording for heart rate variability analysis. Time-domain heart rate variability measures included baseline heart rate, SD of the R-R interval (SDNN), and root mean squared difference of successive R-R intervals (RMSSD). Spectral analysis included sympathetic (low-frequency) and parasympathetic (high-frequency) components. Standardized ACR were calculated from six early morning urine collections using an established algorithm, reflecting age, sex, and duration, and stratified into ACR tertiles, where the upper tertile reflects higher nephropathy risk.

RESULTS

The upper-tertile ACR group had a faster heart rate (76 vs. 73 bpm; $P < 0.01$) and less heart rate variability (SDNN 68 vs. 76 ms, $P = 0.02$; RMSSD 63 vs. 71 ms, $P = 0.04$). HbA_{1c} was 8.5% (69 mmol/mmol) in the upper tertile vs. 8.3% (67 mmol/mol) in the lower tertiles ($P = 0.07$). In multivariable analysis, upper-tertile ACR was associated with faster heart rate ($\beta = 2.5$, 95% CI 0.2–4.8, $P = 0.03$) and lower RMSSD ($\beta = -9.5$, 95% CI −18.2 to −0.8, $P = 0.03$), independent of age and HbA_{1c}.

CONCLUSIONS

Adolescents at potentially higher risk for nephropathy show an adverse cardiac autonomic profile, indicating sympathetic overdrive, compared with the lower-risk group. Longitudinal follow-up of this cohort will further characterize the relationship between autonomic and renal dysfunction and the effect of interventions in this population.

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**The full list of participating AdDIT investigators can be found in the APPENDIX.*

Cardiac autonomic dysfunction is an early subclinical complication of type 1 diabetes (1,2). It is associated with microalbuminuria both in adults and adolescents (3,4) and with the progression of renal disease in adults (5,6). Power spectral analyses of heart rate variability allow more sensitive detection of cardiac autonomic changes than the conventional Ewing battery of tests based on dynamic cardiovascular maneuvers (5,7,8). Recent studies using these modern methods have demonstrated that adverse changes in heart rate variability may be detected during adolescence in people with type 1 diabetes and are primarily associated with poor glycemic control (1,9,10). However, there is a paucity of data on whether cardiac autonomic function is associated with early renal dysfunction before the onset of microalbuminuria.

Nephropathy risk in type 1 diabetes begins with a progressive increase in albumin excretion during adolescence, before the threshold for microalbuminuria is reached (11). Albumin excretion phenotype in children aged between 11 and 15 years, defined by an albumin-to-creatinine ratio (ACR) tertile adjusted for age, sex, and diabetes duration, has been shown to stratify into nephropathy risk (11). Because autonomic neuropathy is a risk factor for progression of renal disease in adults (5,6), we hypothesized that adolescents with type 1 diabetes at higher risk of nephropathy would have an adverse cardiac autonomic profile compared with those at lower risk of nephropathy, independent of glycemic control. We therefore examined heart rate variability in young adolescents with type 1 diabetes stratified for nephropathy risk based on these previously validated ACR tertiles.

RESEARCH DESIGN AND METHODS

Adolescents with type 1 diabetes duration greater than 1 year (n = 445, 49% female, aged 10–17 years) were recruited as part of the nephropathy screening to determine eligibility for the Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial (AdDIT). AdDIT is a multicenter randomized controlled trial across the U.K., Australia, and Canada, where adolescents at risk for diabetic nephropathy, indicated by upper-tertile ACR, are randomized to an angiotensin-converting enzyme (ACE) inhibitor and/or hydroxymethylglutaryl-CoA reductase inhibitor (statin) or placebo (12). Data for the current study were collected before any intervention. The human research ethics committee of each participating center approved this study. Informed consent was obtained from participants and their families.

Participants underwent a 10-min continuous electrocardiogram recording while supine, which was obtained using the LabChart-Pro (ADInstruments, Sydney, New South Wales, Australia). Measurements were taken in a quiet room after the patients had rested for 10 min. All traces were reviewed and analyzed by a single operator masked to patients' clinical status. Traces were checked to ensure R-waves were adequately identified from artifacts and ectopic beats. The term "NN" is used in place of RR to emphasize that the processed beats are normal sinus rhythm (i.e., every QRS complex was preceded by a p-wave). Heart rate variability refers to the variations of heart rate and successive cardiac cycles under the control of the autonomic nervous system. Time-domain measures of overall heart rate variability included mean heart rate, SD of mean NN intervals (SDNN), and root mean squared difference of successive NN intervals (RMSSD). Geometric-domain analysis was performed using triangular index (TI), total number of all NN intervals divided by the height of the histogram of all NN intervals measured on a discrete scale with bins of 7.8125 ms (1/128 s). Frequency-domain measures included low-frequency (LF), defined as $>$0.04 Hz and $<$0.15 Hz, and high-frequency (HF) components, defined as $>$0.15 Hz and $<$0.4Hz, and the LF-to-HF ratio, considered to be an estimate of the relative sympathetic and parasympathetic balance (13). Age-matched community controls (n = 62; 45% female, age range 10–17 years) were contemporaneously recruited from healthy Sydney school-aged adolescents.

All urine samples were analyzed centrally at The WellChild Laboratory at The Evelina Children's Hospital, London. Samples were stored at –70°C before shipping. Urine albumin was measured using laser immunonephelometry (Siemens BN Prospec) and for concentrations $<$2.1 mg/L by an ELISA (14). Urine creatinine was measured using a chromatographic stable isotope dilution electrospray mass spectrometry-mass spectrometry method. For each participant, two time-point ACR measures (mg/mmol), each based on three consecutive early morning samples at two separate visits, were averaged on the log ACR scale. The average residual was calculated using age, sex, and duration and the coefficients from the previously described linear regression model in the Oxford Regional Prospective Study of Childhood Diabetes (ORPS) cohort (11). Upper ACR tertile was assigned to a residual value above 1.2, middle ACR tertile to values between 0.8 and 1.2, and lower ACR tertile to values below 0.8. For this study, the lower two tertiles were combined for analysis.

HbA_{1c} was analyzed locally at each center, using Diabetes Control and Complications Trial (DCCT) aligned methods: HbA_{1c} Variant analyzer (Bio-Rad Laboratories, Hercules, CA), Adams Arkray Inc., (Kyoto, Japan), Vantage analyzer (Siemens Diagnostics, Camberley U.K.), or DCA 2000.

Estimated glomerular filtration rate (eGFR) was calculated from the formula: eGFR (mL/min/1.73 m^2) = 42 $\times$ height (cm)/plasma creatinine (μmol/L) (12). Lipid profile measurements (cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides) were measured using routine laboratory methods.

Height and weight were measured to 0.1 cm and 0.1 kg. Height, weight, and BMI SD scores (SDS) were calculated according to the lambda-mu-sigma (LMS) method (15). Blood pressure was measured using Omran M6 blood pressure (all centers) and/or Dinamap (New South Wales center) monitor using an appropriately sized cuff. Age- and sex-related percentiles and SDS for systolic and diastolic blood pressures were calculated according to published standards (16). Systolic hypertension was defined as systolic blood pressure above the 95th percentile for age and sex.

Statistical Analysis

Descriptive data are summarized as mean $\pm$ SD for parametric data. Heart rate and heart rate variability parameters were normally distributed and analyzed as continuous variables. Urine albumin excretion groups (upper vs. lower two tertiles) were analyzed as

categorical variables. Mean differences between groups were compared using independent samples *t* tests (diabetes vs. control subjects, ACR group upper vs. lower tertiles). Marginal means for the ACR groups (upper vs. lower tertiles) were evaluated at 11, 13, 15, and 17 years of age and compared using ANOVA. Linear regression was used to model the association between ACR group and continuous ACR and heart rate or heart rate variability outcomes. Multivariable regression analysis was used to examine the association between ACR group and other clinical variables (age, HbA_{1c}, blood pressure and BMI SDS, and lipids) with heart rate/heart rate variability outcomes. All statistical analyses were conducted using SPSS version 21 software.

RESULTS

Participant Characteristics

Of the 445 participants who underwent heart rate variability testing, 217 (48%) were in the lower two tertiles for ACR (mean age 14.6 ± 1.5 years) (Table 1). Adolescents in the high-risk (upper tertile) group were slightly younger and had shorter diabetes duration than those in the low-risk (lower tertiles) group. There was no significant difference in sex, HbA_{1c}, or BMI SDS between the two groups. HDL-cholesterol and systolic blood pressure SDS were marginally higher in the upper tertile group. Of the 55 of 445 adolescents with systolic hypertension, 73% were in the upper tertile and 27% were in the lower tertiles ($P < 0.001$).

Standardized ACR as a continuous variable was significantly associated with heart rate ($\beta = 1.5$, 95% CI 0.4–2.7, $P < 0.01$) and RMSSD, a measure of overall heart rate variability ($\beta = -4.4$, 95% CI −8.4 to −0.3, $P = 0.03$), which remained significant after adjusting for age and HbA_{1c}. Systolic and diastolic blood pressures were not significant variables in the model.

Comparison of Heart Rate Variability in the Diabetes Subgroups: Upper ACR Tertile Versus Lower ACR Tertiles

Compared with the lower tertiles, the upper-tertile group had a significantly faster heart rate and lower heart rate variability (SDNN, RMSSD, TI) (Table 2). ACR group remained significantly associated with heart rate, SDNN, and RMSSD in multivariable analysis (Table 3). ACR group was a significant explanatory variable, independent of HbA_{1c}, for heart rate and two measures of overall heart rate variability (SDNN and RMSSD) and was independent of age and HbA_{1c} for heart rate and RMSSD (Table 3).

The marginal means of heart rate and RMSSD for the two ACR groups at four arbitrary age points are graphically represented in Fig. 1, demonstrating the decrease in heart rate and heart rate variability with age.

Compared with controls, adolescents with diabetes had a faster heart rate, lower overall heart rate variability (SDNN, RMSSD, and TI), and higher sympathetic tone (LF-to-HF ratio) compared with age-matched control subjects (Supplementary Table 1) (10).

Table 1—Participant characteristics stratified by urine ACR tertiles

	Lower ACR tertiles	Upper ACR tertile	*P* value
N (% male)	217 (54)	228 (50)	0.45
Age (years)	14.6 (1.5)	14.1 (1.5)	<0.01
SDS			
Height	0.38 (1.06)	0.38 (0.97)	1.00
Weight	0.77 (0.77)	0.67 (0.89)	0.21
BMI	0.67 (0.80)	0.55 (0.90)	0.14
Duration (years)	7.6 (3.4)	6.4 (3.0)	<0.01
HbA_{1c} (%)	8.3 (1.2)	8.5 (1.4)	0.07
HbA_{1c} (mmol/mol)	67 (13)	69 (15)	0.07
eGFR (mL/min/1.73 m^2)	122 (22)	132 (25)	<0.01
Mean SBP (mmHg)	114 (11)	118 (13)	<0.01
Mean DBP (mmHg)	64 (20)	67 (8)	0.09
SBP SDS	0.36 (0.86)	0.78 (1.03)	<0.01
DBP SDS	0.20 (1.88)	0.40 (0.77)	<0.01
Cholesterol (mmol/L)	4.5 (0.9)	4.5 (0.9)	0.64
HDL-C (mmol/L)	1.45 (0.34)	1.54 (0.35)	0.02
LDL-C (mmol/L)	2.5 (0.8)	2.4 (0.7)	0.31
Triglycerides (mmol/L)	1.1 (0.7)	1.2 (0.8)	0.75

Data are presented as mean (SD), except as noted. DBP, diastolic blood pressure; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol; SBP, systolic blood pressure.

CONCLUSIONS

In this multicenter study of young adolescents with type 1 diabetes, we found significant differences in cardiac autonomic profile according to albumin excretion phenotype. Adolescents with a greater risk of later nephropathy also had lower overall heart rate variability and higher resting heart rate compared with those at lower risk of nephropathy, indicating that autonomic dysfunction is associated with future risk of nephropathy before the development of microalbuminuria. Furthermore, it is possible that the autonomic dysregulation contributes to renal dysfunction.

This is the first large-scale study examining heart rate variability in relation to risk of nephropathy in adolescents with type 1 diabetes who have not yet developed microalbuminuria. Reduced heart rate variability has been associated with microalbuminuria in older adolescents (4,9). In the SEARCH for Diabetes in Youth Study, lower SDNN (one measure of overall heart rate variability) was associated with microalbuminuria in older adolescents with type 1 diabetes (mean age 18.8 years, mean duration 9.8 years) (9). In this current study, we found significantly lower SDNN and RMSSD (measures of overall heart rate variability) and faster heart rate in younger adolescents at risk for nephropathy (mean age 14.1 years, mean duration 6.4 years). Adult studies in type 1 diabetes demonstrate an early disturbance in cardiac autonomic function before onset of microalbuminuria. Higher 24-h ambulatory blood pressure and reduced heart rate variability were detected in normoalbuminuric adults with type 1 diabetes with high-normal albumin excretion (above the median of 4.2 μg/min) compared with those with low-normal albumin excretion (17). These changes occurred in the context of significantly worse glycemic control in the group with high-normal albumin excretion; in contrast, our findings were independent of HbA_{1c}.

Table 2—Heart rate variability in adolescents with type 1 diabetes stratified by urine ACR tertiles

HRV parameter	Lower ACR tertiles	Upper ACR tertile	*P* value
HR (bpm)	73 (12)	76 (13)	<0.01
SDNN (ms)	76 (36)	68 (30)	0.02
RMSSD (ms)	71 (49)	63 (43)	0.04
LF power	1,839 (2,282)	1,363 (1,237)	<0.01
HF power	2,439 (3,751)	2,076 (3,229)	0.27
LF-to-HF ratio	1.3 (1.2)	1.5 (1.3)	0.14
TI	17 (7)	15 (6)	0.04

Data are presented as mean (SD). HR, heart rate; HRV, heart rate variability.

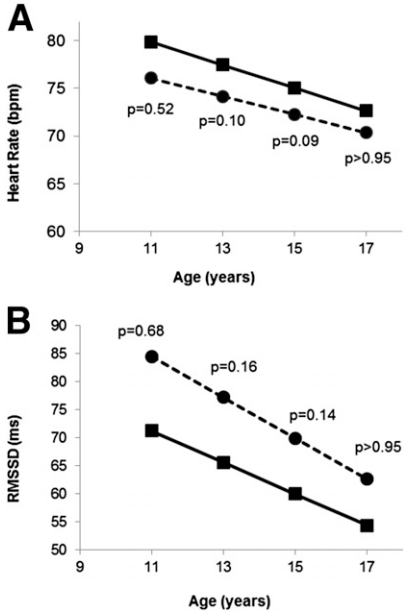

Figure 1—Heart rate (*A*) and overall RMSSD (*B*): marginal means from age 11 to 17 years (●, lower ACR tertiles; ■, upper ACR tertile.)

It is clear that glycemic control contributes to both autonomic dysfunction and other microvascular complications (18). Our study nevertheless demonstrated significant differences in heart rate variability between the two risk groups despite similar mean HbA_{1c}. Furthermore, heart rate, SDNN, and RMSSD remained significant after adjustment for HbA_{1c} in multivariable analysis. However, the association between ACR group and TI, another measure of overall heart rate variability, was weakened after adjustment for HbA_{1c}, suggesting that HbA_{1c} does modify the relationship between some measures of cardiac autonomic dysfunction and albumin excretion.

Obesity has been associated with reduced parasympathetic activity and a relative increase in sympathetic activity in adolescents with and without diabetes (10,19). In contrast, we found that there was no significant difference in BMI SDS in the ACR groups to explain heart rate variance differences between upper and lower ACR tertiles. The lack of difference in BMI SDS in the two groups helps exclude the confounding effect of obesity on autonomic function and albumin excretion in this cohort.

Although systolic and diastolic blood pressures were significantly higher in the upper tertile ACR group in our study, the blood pressure for most of the adolescents in both ACR groups was within the normotensive range for age and sex. Although blood pressure is higher in adolescents with type 1 diabetes with microalbuminuria than in those with normoalbuminuria (20,21), there are mixed data on the detection of higher incident blood pressure before elevation in albumin excretion. In the T1D Exchange Clinic Registry, higher diastolic blood pressure in adolescents was a risk factor for microalbuminuria (22), whereas another study showed that higher incident blood pressure did not precede the onset of increasing albumin excretion (23). High daytime blood pressure may therefore be a relatively late clinical finding in the progression of abnormal albumin excretion.

Ambulatory blood pressure may better predict nephropathy risk in adolescent diabetes than incident blood pressure (21,24). Furthermore, an increase in nocturnal systolic blood pressure preceded the progression to microalbuminuria, and loss of nocturnal dip in blood pressure predicted the development of microalbuminuria in adolescents with type 1 diabetes (25). Because elevation in nocturnal systolic blood pressure and loss of nocturnal blood pressure dip can signify autonomic dysfunction (26), we therefore speculate that autonomic dysfunction may even precede the elevation of ACR into the higher-risk tertile in this young population with type 1 diabetes.

Autonomic dysfunction has been proposed to play a causative role in renal disease through changes in nocturnal glomerular function and renal hemodynamics (6,27) or a loss of protective effect on the kidneys leading to progression of renal disease (6,28,29). Animal data support the role of increased sympathetic activity in the pathogenesis of renal disease (30). A recent study of adults with type 2 diabetes found that cardiac autonomic dysfunction was associated with increased albuminuria and lower eGFR at baseline and also predicted subsequent decline in eGFR (31). Clinical studies in adults with type 1 diabetes have been less clear on the role of cardiac autonomic function on renal decline (28,29,32). In adolescents with type 1 diabetes, there is evidence for autonomic dysregulation occurring early in the pathogenesis of microvascular complications. We previously found that abnormal pupillary

Table 3—Multivariable analysis of heart rate variability outcomes and ACR tertiles

HRV parameter	Factor*	β (95% CI)	*P* value
HR	Upper ACR tertile+	2.5 (0.2–4.8)	0.03
	Age	−1.2 (−1.9 to −0.4)	<0.01
	HbA_{1c}	1.9 (1.0–2.8)	<0.001
SDNN	Upper ACR tertile	−6.6 (−12.7 to −0.4)	0.04
	HbA_{1c}	−3.8 (−6.2 to −1.4)	<0.01
RMSSD	Upper ACR tertile	−9.5 (−18.2 to −0.8)	0.03
	Age	−3.1 (−6.0 to −0.3)	0.03
	HbA_{1c}	−3.9 (−7.2 to −0.5)	0.02

HR, heart rate; HRV, heart rate variability. *Diabetes duration, BMI SDS, and systolic or diastolic blood pressure SDS were not significant explanatory variables in the above models. +Reference group is lower tertiles.

response, a marker of autonomic dysfunction, preceded development of microalbuminuria and diabetic retinopathy 12 years later (33).

A limitation of this study is its cross-sectional nature; thus, it cannot examine causative and temporal relationships between albumin excretion and the autonomic function. Autonomic dysfunction and abnormal albumin excretion may also share common etiology, such as insulin resistance (34,35) and biochemical mediators of inflammation, not formally measured in this study (36–38). Strengths of this study include the large participant recruitment and standardized methodology, heart rate variability analysis by one operator, and careful clinical characterization for eligibility into a follow-up randomized controlled trial (AdDIT).

This study elucidates the adverse heart rate variability profile already present in young adolescents with type 1 diabetes identified to be at higher risk of nephropathy. Longitudinal analysis of these patients will determine possible early predictive value of heart rate variability in addition to albumin excretion phenotype on renal and cardiac outcomes.

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Author Contributions. Y.H.C., M.E.C., and K.C.D. researched the combined data and wrote the manuscript. E.A.D. and T.W.J. researched additional data for their center. T.W.J. and K.C.D. were involved in study concept and design. D.B.D., T.W.J., and K.C.D. were responsible for obtaining funding for the study. All authors (including A.M.C., J.J.C., F.J.C., P.Z.B.-A., and R.N.D.) were involved in data collection and reviewed and edited the manuscript. K.C.D. is the guarantor of this work, and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Appendix

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