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Arterial Stiffness, Lipoprotein Particle Size, and Lipoprotein Particle Concentration in Children with Type 1 Diabetes

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Abstract

OBJECTIVE—To determine if lipoprotein particle abnormalities correlate with arterial stiffness in children with type 1 diabetes (T1D).

STUDY DESIGN—In this case-control study, we evaluated 70 children, 35 with T1D and 35 controls, ages 10–18 years, matched for age, sex, race, and BMI. Arterial stiffness was assessed by radial tonometry (AI_{75}) and blood was collected for lipoprotein subclass analysis.

RESULTS—T1D subjects had increased AI_{75}, decreased small LDL particle concentration (P=0.0067), increased large LDL particle concentration (P=0.007), increased large HDL particle concentration (P=0.0012), increased mean LDL particle size (P=0.0028), and increased mean HDL particle size (P<0.0001) compared to controls. No significant correlations were found between lipoprotein subclasses and arterial stiffness in T1D subjects.

CONCLUSIONS—T1D subjects have increased arterial stiffness when compared to controls, despite a less pro-atherogenic lipoprotein profile, indicating the need to identify other risk factors that correlate with arterial stiffness in T1D youth.

Keywords

Type 1; Adolescents; Children; Arterial Stiffness; Lipoprotein Particles

Type 1 diabetes (T1D) is a well-established risk factor for the development of premature cardiovascular disease (CVD).[1, 2, 3] A multitude of risk factors are independently associated with the increased risk of CVD in T1D, including duration of diabetes, central obesity[4, 5], hypertension,[6] smoking,[4] albuminuria,[4, 7] and dyslipidemia.[8] Nevertheless, the exact pathogenesis of the premature CVD in T1D remains poorly understood.

Although children and adults with reasonably well-controlled T1D (and without nephropathy) have similar or even more favorable lipid profiles than the general population,[9, 10] T1D patients maintain a fourfold higher mortality risk from CVD and have early evidence of arterial stiffness and endothelial dysfunction.[11] While the reasons for this disparity remain unclear, qualitative lipoprotein abnormalities have been documented in adults with T1D,[12] specifically increased small dense LDL (sdLDL) and small dense HDL

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(sdHDL). These abnormalities have been shown to inversely correlate with surrogate markers of arterial dysfunction (brachial reactivity, carotid intima media thickness, and radial artery tonometry).[13, 14] As such, alterations in lipoprotein subclass distributions have been speculated to contribute to the increased CVD risk in these patients.

Although a substantial proportion of children and adolescents with T1D are known to have abnormal serum lipids and alterations in lipoprotein subclass distributions,[15] little is known about the possible relationship between arterial stiffness and lipoprotein particle profiling in children with T1D. Given the low absolute short-term risk for CVD events in children with T1D, many groups, including ours, have attempted to correlate non-invasive surrogate measures of arterial stiffness with classic serum markers of CVD risk.[16] To clarify the specific lipoprotein subclass distribution abnormalities present in children with T1D and to determine if a correlation exists between these and arterial stiffness, we examined serum lipoprotein subfractions and performed radial artery tonometry, as a measure of arterial stiffness, in children with T1D. We hypothesized that T1D subjects would have a more pro-atherogenic lipoprotein profile when compared to age, gender, and body mass index matched controls, and that a direct association would exist between these abnormalities and the increased arterial stiffness previously reported in children with T1D.

Research Design and Methods

We initially studied 98 children with T1D and 57 healthy control subjects. From this group, 43 matched pairs were generated, and from these, blood samples for this analysis were available for 35 matched pairs (21 males and 14 females). The groups were matched for age (±2 years), sex, race, and BMI (±3 kg/m^2). Recruitment processes were described previously by our group.[16] Inclusion criteria for both children with T1D and control subjects were as follows: age between 10 and 18 years and no known cardiovascular disease. Subjects who reported tobacco use, those being treated with anti-hypertensive or lipid-lowering medication, and those with albuminuria/nephropathy were excluded.

The study was approved by the Institutional Review Board of the University of Florida, and all subjects and their families provided consent. Demographic information, medical, exercise, and family history, height, weight, and procedures for obtaining blood were detailed previously.[16]

Measurement of augmentation index (AI) by radial artery tonometry

Radial artery tonometry was performed between 6:00 and 10:00 A.M. with the child supine and relaxed. Study subjects were required to fast after midnight and to abstain from caffeine for 24 h before the study. Augmentation index (AI) and AI corrected to a as described previously.[16] Briefly, a high-fidelity heart rate of 75 (AI_{75}) were measured micromanometer with a frequency response of 2 kHz (Millar Instruments, Houston, TX) was placed on the right radial artery, and gentle pressure was applied until a consistent waveform was produced. After 10–20 sequential waveforms had been acquired, the integral software was used to generate an averaged peripheral and corresponding central waveform that was used for the determination of the AI and AI_{75}. The amplitude and timing of the reflected wave depends largely on the stiffness of the small and large arteries; thus, AI provides a measure of systemic arterial stiffness. AI_{75} allows for improved intersubject comparison of central aortic pressure by accounting for differences related to heart rate variation. An elevated or positive AI suggests stiffer arteries than a low or negative AI.

Serum lipids, blood HbA_{1c}, and plasma glucose

Serum was collected from study participants with Vacutainer serum separator tubes (BD Biosciences, San Diego, CA). After collection, samples to be analyzed for lipids, HbA_{1c},

and glucose were immediately refrigerated and transported to the Shands Hospital laboratory at the University of Florida. Samples were analyzed in the clinical laboratory using standard technique, and the remaining serum was then frozen (−70°C). Frozen samples from 35 matched pairs of subjects were then analyzed with proton NMR spectroscopy, using *NMR LipoProfile*-II (LipoScience, Raleigh, North Carolina) to measure the particle concentrations of 10 subclasses of VLDL, LDL and HDL. The NMR method exploits the fact that each lipoprotein subclass particle in plasma of a given size broadcasts its own characteristic lipid methyl group NMR signal. The measured amplitudes of these signals are directly proportional to the subclass particle concentrations. In addition, *NMR LipoProfile*-II calculated values for mean VLDL, LDL, and HDL particle size, and estimates of total LDL-c and VLDL-c, triglycerides, and HDL-c were recorded.

Statistical considerations

Using a matched pair design, case-control comparisons were assessed with one-sample paired *t* tests for the following dependent variables: lipoprotein subclass particle concentration and size. All *P* values were two-sided. The primary dependent variables were Large LDL particle concentration and mean LDL size. To determine if a difference existed in large LDL particle concentration and mean LDL size between the patients with T1D (n =35) and their matched controls, the study had 80% two-sided power at P = 0.025 (0.05/2) to detect a difference of 0.49 SD. Sensitivity was to 197 for LDL (total) particle concentration and to 0.37 for LDL mean particle size. Analyses for associations between AI_{75} and LDL particle concentration and size were conducted separately within control subjects and T1D case subjects using Pearson's correlation. The study had 80% power, at P=0.05 two-sided to detect a Pearson Correlation Coefficient of ≥0.45 in absolute value.

Results

Laboratory, anthropometric, and tonometry characteristics of the matched T1D and control groups are shown in Table 1. Lipoprotein particle concentration and mean particle size of the matched groups are shown in Table 2. Pearson correlations of AI_{75} with lipoprotein particle concentration and mean particle size are shown in Table 3.

LDL Particle Concentration and Size

Although total LDL particle concentration did not significantly differ between T1D subjects and controls, differences existed in the LDL particle subclass concentrations (Table 2). Using a paired difference two-sided t test, large LDL particle concentration was greater in T1D subjects than in controls (P = 0.007) whereas controls had significantly higher small LDL (P = 0.0067), medium/small LDL (P = 0.0026), and very small LDL particle concentration (P = 0.0091) than T1D subjects. The LDL particle size was larger in T1D subjects than controls (P = 0.0028).

HDL Particle Concentration and Size

Large HDL particle concentration was higher in patients with T1D (P = 0.0012) and small HDL particle concentration was higher in the control subjects (P = 0.028) (Table 2). However, there were no statistically significant differences in total HDL particles concentration or medium HDL particle subclass concentrations between the two groups. The mean HDL particle size was significantly larger in the T1D subjects (<0.0001).

VLDL and Chylomicron Particle Concentration and Size

T1D subjects had a lower total VLDL and chylomicron particle concentration than the control population (Table 2). VLDL mean particle size did not significantly differ between the two groups (P= 0.94).

Associations Between AI_{75} and Lipid Particle Concentration and Size

There was no significant correlation between total LDL particle concentration, any of the LDL particle subclass concentrations, or LDL mean particle size and AI_{75} in the T1D subjects (Table 3). In the control subjects, however, both total LDL and HDL particle concentration positively correlated with AI_{75}, with coefficients of variation of 0.35 (P = 0.0412) and 0.45 (P = 0.0068), respectively (Table 3).

Associations Between HbA1c and Lipid Particle Concentration and Size

A post-hoc, hypothesis generating analysis was performed to identify possible correlations between HbA1c and lipoprotein concentration and size and found no significant correlation between HbA1c and small LDL particle concentration (r= −0.02, p=0.9), total LDL particle concentration (r=0.26, p=0.11), and mean LDL particle size (r=−.22, p=0.19).

Discussion

Our study is the first to date to examine the relationship between lipoprotein subclass analysis and surrogate markers of arterial stiffness in children with T1D and matched controls. We previously observed increased arterial stiffness in children with T1D but found no correlation between arterial stiffness and traditional CVD risk markers. We therefore speculated that alterations in lipoprotein particle subclass distributions might account for differences in arterial stiffness in youth with T1D and age, sex, and BMI matched controls. Despite the fact that children with T1D had evidence of arterial stiffness, we found lipoprotein size and particle concentration to be less classically “pro-atherogenic” in children with T1D than in matched controls. Specifically, children with T1D had 1) more large LDL particles, 2) fewer small, medium-small, and very small LDL particles, 3) larger mean LDL particle size, 4) lower total VLDL-c concentration, 5) fewer large and medium VLDL particles, 6) more large HDL particles and 7) larger mean HDL particle size than controls. Furthermore, we found no significant correlation between any of the lipoprotein particle subclass concentrations or mean particle sizes and arterial stiffness (measured as AI_{75}) in the T1D subjects. As expected, a positive correlation was found between AI_{75} and total LDL-c, total HDL-c, and both large and small HDL particle concentration in control subjects, indicating other factors must be playing a role in the arterial dysfunction observed in T1D.

Previous analyses of lipoprotein particle subclass distributions in children with T1D compared to non-diabetic controls have provided conflicting results. Ohta et al[21] reported significantly greater HDL and LDL particle sizes in T1D children compared to healthy control subjects. In contrast, Alabakovska et al[22] showed that despite an absence of significant differences in the plasma lipid profiles between T1D children and controls, the concentration of sdLDL was increased and mean LDL particle size was smaller in subjects with T1D. The SEARCH Case-Control study compared healthy controls with T1D subjects between the ages of 10–22 years (n=512, HbA1c<7.5%, mean diabetes duration 4.22 years).[10] The T1D subjects had 1) similar total LDL-c and LDL mean particle size, 2) higher HDL-c, 3) lower triglycerides, and 4) increased sdLDL particle number. Although T1D youth frequently have “normal” lipid profiles, they have alterations in lipoprotein particle subfractions. Data regarding the exact nature of these lipoprotein subclass differences is

conflicting, and their contribution to the increased CVD risk present in these patients, evidenced by the results of the current study, is not yet certain.

The question thus arises, "which childhood risk factors are predictive of future CVD?" In this cohort, the lack of correlation between lipoprotein particle concentration / number and AI_{75} implies that other T1D-associated abnormalities, such as hypertension, albuminuria, or perhaps most importantly, chronic hyperglycemia, likely contribute more directly to arterial stiffness than lipid parameters. Still, our previous analyses found no correlation between HbA1c and despite having no albuminuria and both systolic (mean 8.4%) and AI_{75} in the T1D children and diasotolic blood pressures lower than control subjects, our T1D cohort had increased arterial stiffness.[16] Furthermore, a post-hoc, hypothesis generating analysis of these data found no significant correlation between HbA1c and very small LDL particle concentration, total LDL particle concentration, and mean LDL particle size. As such, other markers of hyperglycemia, such as advanced glycation end-products (AGEs) and their receptor (RAGE), reported to play an important role in the development of T1D vascular complications, should be considered in future efforts to explain the vascular dysfunction seen in youth with T1D. [17, 18]

Despite the novel findings provided by this study, important limitations require discussion. The inherent variability of the augmentation index as a measure of overall vascular function may indicate that a composite of surrogate markers, and not just one, is needed to accurately assess long term CVD risk in children. As such, the relatively small sample size of our cohort did not provide adequate power to evaluate the relationship between AI_{75} and lipoprotein particle subfractions in those children with the most severe vascular dysfunction. Similarly, the size of our cohort may account for differences between our observations regarding LDL particle concentration and size in children with T1D and those from larger cohorts.[10] Also, because much of these data were collected in a diabetes camp setting, pubertal staging was not included in the protocol. While children were matched for age and gender, the potential differential effects of puberty on arterial stiffness and lipid profiling could not be assessed. Last, control subjects whose physicians or family perceived them as being at increased risk for CVD may have been more inclined to participate resulting in a control group with higher background CVD risk.

In summary, our study is the first to assess correlations between lipoprotein particle subclasses and arterial stiffness in children with T1D and suggests that T1D in children is not associated with classically pro-atherogenic lipoprotein subclass distributions. Although the T1D subjects in our study had stiffer arteries than controls, their lack of pro-atherogenic lipoprotein subclass levels as well as the inability to demonstrate a correlation between lipoprotein profiles and increased AI_{75} in children with T1D requires further investigation. The cause of the early increase in arterial stiffness in children with T1D remains uncertain. Future studies examining larger patient populations and those with the most severe abnormalities in vascular function may prove helpful in clarifying associations between lipoprotein particle subfractions and CVD risk. The elucidation of risk factors that correlate with arterial stiffness in children with T1D should aid clinicians in identifying those children at the highest risk for CVD, potentially allowing for early targeted intervention and thus primary prevention of CVD-associated morbidity and mortality.

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List of Abbreviations

AGE	Advanced glycation end product
AI_{75}	Radial augmentation index (corrected to a heart rate of 75)
BMI	Body mass index
CVD	Cardiovascular disease
HDL-c	HDL cholesterol
LDL-c	Low density lipoprotein cholesterol
RAGE	Receptor for advanced glycation end products
sdHDL	small, dense high density lipoprotein
sdLDL	small, dense low density lipoprotein
T1D	Type 1 diabetes
VLDL-c	Very low density lipoprotein cholesterol

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Table 1

Matched type 1 diabetic subjects and control subjects (n = 35)

	T1D subjects	Control subjects	Paired Difference	P
HbA1c (%)	**8.41 ± 1.29**	**5.2 ± 0.25**	**3.17 ± 1.23**	**<0.0001**
Total cholesterol (mg/dL)	155.7 ± 29.7	154.3 ± 38.0	2.3 ± 44.4	0.76
Triglycerides (mg/dL)	63.7 ± 28.7	96.4 ± 59.0	**−32.1 ± 72.5**	**0.014**
HDL (mg/dL)	**57.0 ± 8.5**	**51.7 ± 12.5**	**5.8 ± 15.6**	**0.038**
LDL(mg/dL)	89.4 ± 35.8	88.7 ± 24.7	0.6 ± 38.9	0.92
Systolic BP (mmHg)	**110.7 ± 13.2**	**116.3 ± 9.7**	**−5.5 ± 12.7**	**0.014**
Diastolic BP (mmHg)	**68.1 ± 9.1**	**72 ± 8.5**	**−3.9 ± 10.4**	**0.031**
Age (years)	13.2 ± 1.2	13.5 ± 2.1	−0.3 ± 1.2	
BMI (SDS)	0.9 ± 0.8	0.95 ± 1.1	−0.05 ± 0.53	
Height (SDS)	0.3 ± 0.7	0.5 ± 1.0	−0.2 ± 1.15	

Data are Mean ± SD.

Bold face indicates significance

Table 2

Matched T1D and Control Subjects: Mean Lipoprotein Particle Concentration and Mean Particle Size (n = 35)

	T1D Subjects	Control Subjects	Paired Difference	P
Mean Particle Concentration *				
Total VLDL and Chylomicron	**36.9 ± 22.5**	**49.9 ± 19.1**	**−12.9 ± 25.7**	**0.0053**
Large VLDL and Chylomicron	**0.37 ± 0.35**	**1.06 ± 0.75**	**−0.69 ± 0.82**	**<.0001**
Medium VLDL	**8.39 ± 7.59**	**14.1 ± 7.12**	**−5.74 ± 8.86**	**0.0005**
Small VLDL	28.2 ± 16.8	34.7 ± 13.6	−6.49 ± 18.8	**0.048**
Total LDL	770 ± 266	796 ± 258	−25.6 ± 395	0.70
IDL	37.1 ± 31.8	28.7 ± 26	8.4 ± 37	0.19
Large LDL	**424± 200**	**323 ± 95**	**100 ± 206**	**0.007**
Small LDL	**310 ± 162**	**444 ± 215**	**−134 ± 275**	**0.0067**
Medium small LDL	**57 ± 29.5**	**85.0 ± 43.8**	**−28.0 ± 50.9**	**0.0026**
Very small LDL	**252 ± 135**	**359 ± 173**	**−106 ± 227**	**0.0091**
Total HDL	23.4 ± 6.04	23.9 ± 6.95	−0.52 ± 8.33	0.72
Large HDL	**7.22 ± 2.46**	**5.27 ± 2.26**	**1.95 ± 3.26**	**0.0012**
Medium HDL	1.93 ± 1.63	2.16 ± 1.86	−0.22 ± 2.48	0.60
Small HDL	14.2 ± 4.06	16.5 ± 5.01	−2.24 ± 6.15	**0.038**
Mean Particle Size (nm)				
VLDL	48.6 ± 13.0	48.5 ± 6.41	0.16 ± 13.2	0.9434
LDL	**21.7 ± 0.62**	**21.3 ± 0.52**	**0.40 ± 0.74**	**0.0028**
HDL	**9.49 ± 0.35**	**9.05 ± 0.38**	**0.45 ± 0.53**	**<.0001**

Date are mean ± SD;

BOLD indicates significance at P<0.05, two sided.

* LDL, VLDL, and Chylomicron concentrations are nmol/L. HDL concentrations are μmol/L

Table 3

Pearson Correlations in T1D and Control Subjects Between AI_{75} and Mean Lipoprotein Particle Concentration and Mean Particle Size

	T1D subjects r (P)	Control subjects r (P)
Mean Particle Concentration		
VLDL and Chylomicron (total)	0.14 (0.42)	0.098 (0.58)
Large VLDL and Chylomicron	−0.1 (0.58)	−0.04 (0.82)
Medium VLDL	−0.22 (0.19)	−0.13 (0.46)
Small VLDL	−0.13 (0.44)	0.21 (0.23)
LDL (total)	−0.26 (0.13)	**0.35 (0.04)**
IDL	0.05 (0.79)	0.22 (0.19)
Large LDL	−0.22 (0.19)	0.15 (0.38)
Small LDL	−0.16 (0.36)	0.32 (0.06)
Medium small LDL	−0.04 (0.84)	0.32 (0.06)
Very small LDL	−0.18 (0.3)	0.32 (0.06)
HDL (total)	−0.14 (0.43)	**0.45 (0.01)**
Large HDL	−0.16 (0.35)	**0.39 (0.02)**
Medium HDL	0.11 (0.53)	0.17 (0.34)
Small HDL	−0.15 (0.4)	**0.39 (0.02)**
Mean Particle Size		
VLDL	0.08 (0.63)	−0.20 (0.24)
LDL	−0.12 (0.47)	−0.23 (0.18)
HDL	0.07 (0.71)	−0.09 (0.59)

BOLD indicates significance