Radial Artery Tonometry Demonstrates Arterial Stiffness in Children With Type 1 Diabetes

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OBJECTIVE — To determine if children with type 1 diabetes have increased arterial stiffness by estimating augmentation index with the simple noninvasive technique of radial artery tonometry.

RESEARCH DESIGN AND METHODS — We studied 98 type 1 diabetic children and 57 healthy control subjects, ages 10–18 years, matched for age, sex, race, and BMI, generating 43 matched pairs. Radial artery tonometry was performed, and blood was collected for analysis of fasting lipids, HbA_{1c}, glucose, and cytokines in all children.

RESULTS — Children with diabetes had a significantly higher augmentation index corrected to a heart rate of 75 (AI_{75}) than their matched control subjects. Mean AI_{75} in type 1 diabetic subjects was 1.11 ± 10.15 versus -3.32 ± 10.36 in control subjects. The case-control difference was 5.20 ± 11.02 ($P = 0.0031$).

CONCLUSIONS — Children with type 1 diabetes have increased arterial stiffness compared with healthy control subjects. Radial artery tonometry is a simple noninvasive technique that could be added to the armamentarium of tests used to provide cardiovascular risk stratification in children with type 1 diabetes.

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Type 1 diabetes is an important risk factor for cardiovascular disease. Other cardiovascular risk factors related to diabetes include long duration of disease, poor metabolic control, and coexisting hypertension or dyslipidemia. The Diabetes Control and Complications Trial demonstrated that long-term glycemic control is critical in reducing the risk of type 1 diabetes–related microvascular and, possibly, macrovascular complications (1).

Many adult studies have demonstrated that the incidence of cardiovascular events can be lessened with reduction of plasma cholesterol and optimal management of hypertension. Unfortunately, the majority of patients who are being treated aggressively have already manifested cardiovascular complications. Because efficacy of intervention in children cannot be measured by cardiovascular event end points, surrogate markers must be used. Brachial artery reactivity is a technique that measures the endothelium-dependent dilation of the brachial artery in response to reactive hyperemia. In patients with endothelial dysfunction, the ability of the artery to dilate is impaired. Endothelial dysfunction, as measured by decreased brachial reactivity, has been shown to be an independent predictor of cardiovascular events (2). Impaired brachial reactivity has been demonstrated in adults and in a small group of children with type 1 diabetes (3,4).

Recent studies have demonstrated that endothelial function, as measured by brachial reactivity and carotid intima-medial thickness (IMT), are abnormal in children with type 1 diabetes (5); however, no one has yet demonstrated if radial tonometry can provide similar results. Because radial tonometry can be performed in nearly any clinic setting, is easy and affordable to perform, and provides the user with instant analysis of the patient's arterial stiffness, tonometry has a potential advantage over brachial reactivity and carotid IMT as a clinically useful tool.

To test the utility of radial tonometry, we studied whether children with type 1 diabetes had increased arterial stiffness, as measured by augmentation index (AI), when compared with healthy control subjects. To gain further insight into their cardiovascular risk profiles, we obtained historical data on family history, exercise, and glycemic control and obtained blood for lipid, glucose, HbA_{1c}, and cytokine analysis.

RESEARCH DESIGN AND METHODS

— We studied 98 children with type 1 diabetes and 57 healthy control subjects. From this group, 43 matched pairs were generated. The groups were matched for age (±2 years), sex, race, and BMI (±3 kg/m^2). Children were recruited from the Florida Diabetes Camp, the University of Florida diabetes and primary care clinics, and general pediatrics practices in the area. Children with type 1 diabetes were recruited by letters sent to the parents of all children reg-

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Abbreviations: AI, augmentation index; AI_{75}, augmentation index corrected to a heart rate of 75; hsCRP, high-sensitivity C-reactive protein; IL, interleukin; IMT, intima-medial thickness.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

istered for diabetes camp offering free lipid and HbA_{1c} analyses in return for participation. Control subjects were recruited from general pediatrics practices by letters sent to the parents of clinic patients offering free analyses of lipids, glucose, and HbA_{1c} in return for participation. While children with type 1 diabetes would likely have been routinely tested for lipids, glucose, and HbA_{1c}, healthy control subjects would not. Thus, excluding diabetes, there may have been differences in background cardiovascular risk between case and control subjects because control subjects whose physician or family perceived them as being at increased risk may have been more inclined to participate. Inclusion criteria for both children with diabetes and control subjects were as follows: age between 10 and 18 years, no known cardiovascular disease, and no history of using antihypertensive or lipid-lowering medications. Children with diabetes were included only if they had been diagnosed for at least 1 year. Children were classified as having type 1 diabetes based on a history of acute onset of polyuria, polydipsia, polyphagia, weight loss, and ketosis. When history was not clear, autoantibody status was used to confirm type 1 diabetes. There were no children with diabetes included that did not have either a well-documented history or at least one positive diabetes-related autoantibody.

The study was approved by the Institutional Review Board of the University of Florida. Subjects' parents provided written consent before their child was enrolled in the study, and the subjects provided assent. Subjects' parents completed a brief questionnaire that included age, race, medications, family history, most recent HbA_{1c}, length of diagnosis, level of exercise, and history of recent illnesses. Family history was specified in the questionnaire as pertaining to only first- and second-degree relatives of the child, and definitions of hypercholesterolemia, hypertension, and early heart disease were provided. Level of exercise was graded on a scale of one to four.

Radial artery tonometry was performed and blood samples were obtained 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. Height was measured on a wall-mounted stadiometer (Genentech, San Francisco, CA), and weight was read from a digital scale. After a 5-min rest in the supine position, the subjects had their blood pressure measured with a digital oscillometric device (Omron model HEM-739; Omron Healthcare, Vernon Hills, IL). Radial tonometry was then performed. After the completion of the radial tonometry, blood was obtained for glucose, HbA_{1c}, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, high-sensitivity C-reactive protein (hsCRP), interleukin (IL)-1β, and IL-6. Subjects with type 1 diabetes had their morning insulin injection postponed until all studies were completed.

Measurement of augmentation index by radial tonometry

AI and AI corrected to a heart rate of 75 (AI_{75}) were measured using the SphygmoCor Vx version 7.01 (AtCor Medical, Sydney, Australia). In brief, a high-fidelity 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 algorithm used to convert the radial pulse wave to an aortic waveform was derived from invasive pressure and flow data obtained by cardiac catheterization and has been validated in several adult studies (6–8). A quality index is displayed and represents reproducibility of the waveform. A value of >70 is considered to demonstrate excellent waveform consistency. For this study, only measurements with a quality index >80 were accepted. Two acceptable measurements were obtained on each subject. AI is defined as the difference between the first and second peaks of the central arterial waveform, expressed as a percentage of the pulse pressure, and measures the contribution that the wave reflection makes to the arterial pressure waveform. 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 a true comparison of the augmentation of central pressure between study subjects by discounting differences related to heart rate variation (9). 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 lipid, 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.

Cytokines

Serum for cytokine and autoantibody analysis was separated into serial aliquots and frozen at −80°C. All serum analyses were conducted after a single freeze-thaw cycle. Cytokine measurements from serum were performed using a commercially available multiplexed kit (Beadlyte Human Multi-Cytokine Detection System 3; Upstate, Lake Placid, NY) and the Luminex^{100} LabMAP System. Quantitative evaluation of the serum cytokines IL-1β and IL-6 was performed. Serum samples were subjected to a 1:2 dilution in serum diluent provided by the manufacturer to reduce the effects of interfering heterophile species (10,11). hsCRP (Alpco, Windham, NH) levels were measured by standard sandwich enzyme-linked immunosorbent assay techniques according to manufacturer's instructions. Serum analyte concentrations were calculated using four-parameter analysis using SoftMax Pro Software, version 2.2.1 (Molecular Devices, Sunnyvale, CA).

Serum autoantibody detection

Autoantibodies against two type 1 diabetes–associated autoantigens were tested from serum obtained from all study participants, including those against GAD65 and insulinoma-associated protein 2. Assays were performed as previously described (11). The investigators are regular participants in workshops and proficiency tests sponsored by the Immunology of Diabetes Society and the Centers for Disease Control and Prevention to validate assay performance. At the most recent effort (Diabetes Autoantibody Standardization Program 2003), our performance for GADA assay indicated 80% sensitivity/95% specificity for type 1 dia-

Table 1—*Matched type 1 diabetic subjects and control subjects (n = 43)*

	Type 1 diabetic subjects	Control subjects	Paired difference	*P*
AI	1.11 ± 10.15	−0.47 ± 9.79	1.59 ± 11.61	0.37
AI_{75}	**1.88 ± 10.75**	**−3.31 ± 10.36**	**5.20 ± 11.02**	**0.0031**
HbA_{1c}	**8.41 ± 1.29**	**5.2 ± 0.25**	**3.17 ± 1.23**	**<0.0001**
Total cholesterol	151.19 ± 29.46	152.66 ± 36.1	−5.12 ± 35.72	0.35
Triglycerides	**61.05 ± 26.32**	**89.36 ± 54.72**	**−25.0 ± 62.60**	**0.012**
HDL	56.67 ± 8.2	53.09 ± 12.26	4.05 ± 15.43	0.093
LDL	85.18 ± 34.1	86.02 ± 25.25	−4.09 ± 32.31	0.41
Glucose	**159.67 ± 68.78**	**85.22 ± 9.58**	**75.89 ± 70.18**	**<0.001**
Systolic blood pressure	**109.93 ± 13.6**	**115.02 ± 10.31**	**−5.09 ± 14.51**	**0.025**
Diastolic blood pressure	**67.45 ± 8.8**	**71.18 ± 7.96**	**−3.73 ± 9.80**	**0.015**

Data are means ± SD. Bold face indicates significance.

betes, whereas our insulinoma-associated protein 2 antigen assay provided 64% sensitivity/100% specificity.

Statistical consideration

As described above, the study was planned as a matched pair design. However, if matching factors are treated as covariates, all conclusions qualitatively remained the same when analysis was performed on all entrants, independent of match availability. When analyzing the matched pairs, case-control comparisons were assessed with one-sample paired *t* tests for the following dependent variables: AI and AI_{75} (primary) and total cholesterol, HDL, LDL, triglycerides, blood pressure, HbA_{1c}, and glucose (secondary). All *P* values were two-sided. The original study was planned for a sample size of 100 matched pairs. However, recruitment of matched control subjects within the planned time frame was not feasible. Fortunately, the matched variations in the variables AI and AI_{75} were somewhat smaller than anticipated, and a retrospective power calculation, using matched SDs of 11.6 and 11.0, respectively, demonstrates that the actual sample size of 43 matched pairs yields sensitivity to differences in the paired means of 5.6 and 5.3, respectively, at $P = 0.025$ (half of 0.05) two-sided and 80% power.

As a secondary objective, separate analyses for associations with AI and AI_{75} were conducted within control subjects ($n = 57$) and type 1 diabetic case subjects ($n = 98$). Because of the potential for outliers in hsCRP and the qualitative nature of some of the variables, Spearman's correlation was used to examine the relationship between AI and AI_{75} and total cholesterol, LDL, HDL, triglycerides, blood pressure, HbA_{1c}, glucose, hsCRP, IL-1, IL-6, family history, and exercise regimen.

RESULTS — Laboratory and tonometry characteristics of the matched diabetes and control groups are shown in Table 1. Spearman correlations of AI and AI_{75} are shown in Table 2.

AI

Type 1 diabetes was associated with increased arterial stiffness as evidenced by the higher AI_{75}. The mean AI_{75} in type 1 diabetic subjects was 1.89 ± 10.75, whereas the AI_{75} for control subjects was −3.32 ± 10.36. Using a paired difference two-sided *t* test, the AI_{75} demonstrated a case-control difference of 5.2 ± 11.0 ($P = 0.003$). There was no significant difference in the uncorrected AI ($P = 0.37$).

Lipids

Total cholesterol, LDL, and HDL analyses did not reveal any significant case-control differences. Triglyceride levels, however, were significantly higher in the control

Table 2—*Spearman correlations in type 1 diabetic subjects and control subjects*

	Type 1 diabetic subjects ($n = 98$)		Control subjects ($n = 57$)	
	AI (*P*)	AI_{75} (*P*)	AI (*P*)	AI_{75} (*P*)
HbA_{1c}	0.076 (0.46)	0.089 (0.39)	0.060 (0.66)	0.094 (0.49)
Total cholesterol	0.055 (0.60)	0.056 (0.59)	0.150 (0.27)	0.198 (0.14)
Triglycerides	0.096 (0.35)	0.061 (0.55)	0.018 (0.89)	0.046 (0.73)
HDL	−0.027 (0.80)	0.086 (0.41)	0.192 (0.15)	0.126 (0.35)
LDL	0.062 (0.54)	−0.013 (0.89)	0.071 (0.16)	0.076 (0.58)
Glucose	0.164 (0.11)	0.132 (0.20)	0.004 (0.97)	−0.0004 (0.997)
Systolic blood pressure	−0.132 (0.20)	−0.144 (0.15)	−0.289 (0.03)	−0.169 (0.21)
Diastolic blood pressure	0.094 (0.36)	0.094 (0.35)	−0.059 (0.66)	0.058 (0.67)
IL-1β	−0.190 (0.06)	−0.079 (0.44)	0.210 (0.12)	0.010 (0.46)
IL-6	−0.150 (0.14)	−0.126 (0.22)	−0.152 (0.26)	−0.074 (0.59)
hsCRP	−0.005 (0.96)	0.004 (0.96)	0.059 (0.66)	0.133 (0.33)
Family history of hypertension	0.120 (0.24)	0.149 (0.14)	−0.114 (0.44)	−0.066 (0.63)
Family history of early cardiovascular disease	−0.031 (0.44)	−0.078 (0.45)	**0.345 (0.0086)**	**0.381 (0.0034)**
Family history of elevated cholesterol	−0.132 (0.20)	−0.101 (0.33)	0.303 (0.02)	0.218 (0.10)
Exercise	0.027 (0.79)	0.032 (0.76)	**−0.346 (0.0083)**	**−0.449 (0.0005)**
Years of diabetes	0.041 (0.44)	0.080 (0.44)	NA	NA

Bold face indicates significance.

population with a case-control difference of -25.0 ± 62.6 ($P = 0.012$). Even when lipid values among only the type 1 diabetic subjects were analyzed, no significant associations were noted between total cholesterol, LDL, HDL, or triglycerides and either AI or AI_{75} (Table 2).

Blood pressure

Systolic and diastolic blood pressure analysis revealed significantly higher values in the control subjects, with differences of -5.2 ± 14.6 ($P = 0.025$) and -3.67 ± 9.9 ($P = 0.019$), respectively. However, no significant associations were noted between systolic or diastolic blood pressure and AI or AI_{75} (Table 2).

Length of diabetes and control

Duration of diabetes, HbA_{1c}, and blood glucose did not demonstrate a significant association with AI or AI_{75} (Table 2). Because of the lack of substantive variation in ages, the study was not adequately powered to determine if the difference in AI or AI_{75} between control subjects and type 1 diabetes subjects became apparent at a specific age.

Cytokines

There were no significant associations between AI or AI_{75} and IL-1, IL-6, or hsCRP (Table 2).

Exercise

Reported exercise level among type 1 diabetic case subjects failed to demonstrate a significant correlation with AI or AI_{75}. Reported exercise level among control subjects alone did however reveal a significant association with both AI ($r = -0.44$, $P < 0.001$) and AI_{75} ($r = -0.33$, $P = 0.015$) (Table 2).

Family history

Among type 1 diabetic case subjects, family history failed to demonstrate a significant correlation with either AI or AI_{75}. Among control subjects, significant associations were seen between AI and family history of hypercholesterolemia ($r = 0.29$, $P = 0.030$, for AI) and early heart disease ($r = 0.38$, $P = 0.004$, for AI; $r = 0.42$, $P = 0.001$, for AI_{75}), but not family history of hypertension (Table 2).

Sex

The case-control difference among paired females demonstrated a significant difference in mean AI_{75}. Case-control difference of mean AI_{75} among paired males did not reveal any significant differences. Although the case-control difference between AI_{75} in matched females reached significance and the difference between matched males did not, there was no significant difference between males and females. Hence, the overall conclusion should take precedence over the sex-specific conclusion.

CONCLUSIONS — This study confirms that children as young as 10 years of age with type 1 diabetes have increased arterial stiffness when compared with matched control subjects. Although several recent studies present similar findings (4,5,12,13), this is the first study to use radial artery tonometry and AI to demonstrate increased arterial stiffness in children with type 1 diabetes.

Arterial stiffness as a result of endothelial dysfunction is an early sign of cardiovascular disease and occurs more often and at an earlier age in patients with type 1 diabetes compared with those without diabetes. Endothelial dysfunction in type 1 diabetes is primarily due to increased production of advanced glycation end products, causing decreased production and action of nitric oxide and a concomitant decrease in arterial compliance (14). The resultant endothelial dysfunction allows for premature integration of lipid-laden macrophages in arterial walls. In addition, the hyperglycemic environment results in qualitative changes in LDL particle size, oxidation, and glycation that have been implicated in early increases in carotid artery IMT and endothelial dysfunction (15,16). Despite the fact that most type 1 diabetic patients in reasonable metabolic control have normal cholesterol profiles, decreasing these modified LDLs may be a plausible intervention to reduce cardiovascular disease in type 1 diabetes. Decreasing LDL values in relatively young type 1 diabetic patients (average age 34 years) with normal initial LDL values resulted in improved endothelial function after just 6 weeks of statin therapy (17).

Because management of hyperglycemia is the cornerstone of therapy in type 1 diabetes, it is often assumed that optimization of glucose control is all that is necessary to minimize the risk of macrovascular disease. However, even the Diabetes Control and Complications Trial's intensive therapy group (average HbA_{1c} of 7.2%), while showing improved carotid IMT when compared with the conventional treatment group (average HbA_{1c} 9.1%), had significantly increased carotid IMT compared with control subjects (18,19). This difference correlated significantly with blood pressure and cholesterol levels (20). Optimal management of all comorbidities is needed to minimize risk.

Nevertheless, many clinicians believe that diabetes-related cardiovascular risk is not sufficiently affected by metabolic derangements in childhood to pursue optimal management of lipids and hypertension in children with type 1 diabetes. Data from the Pittsburgh Epidemiology of Complications Study, a 10-year follow-up of patients who developed type 1 diabetes before the age of 17 years, showed that high blood pressure and increased LDL were independent risk factors for microvascular disease, macrovascular disease, and mortality (21). Autopsy studies of over 3,000 children found that children have evidence of aortic fatty streaks as early as 3 years of age and raised fibrous plaques as early as 8 years of age (22,23). The Muscatine Heart Study and the Bogalusa Heart Study have demonstrated that cardiovascular risk factors apparent in childhood predict future coronary artery disease (24,25).

Radial artery tonometry is an easily learned, affordable, noninvasive, reproducible, and accurate technique that can be used to monitor arterial stiffness and, therefore, future cardiovascular risk in both high-risk children and adults (3,26–28). Radial artery tonometry has been shown to have excellent intra-observer and intra-patient reproducibility and to provide a reliable assessment of endothelial dysfunction (29,30). In adults with type 1 diabetes, AI is increased prematurely (27).

This is the first study to evaluate radial artery tonometry in children with type 1 diabetes. Although we were unable to show any significant correlations between AI in children with type 1 diabetes and established cardiovascular risk factors, it is possible that the type 1 diabetic children with the most elevated AIs might have demonstrated correlations if the study had been adequately powered to evaluate these relationships.

Using a combination of flow-mediated dilation and carotid IMT, Singh et al. (4) and Jarvisalo et al. (5) demon-

strated endothelial dysfunction in children with type 1 diabetes. Both studies revealed correlations with endothelial dysfunction and LDL cholesterol. The two studies disagreed, however, when describing the relationship between increased carotid IMT and type 1 diabetes. While the disparate findings may be explained by differences in technique, it is possible that the differences are related to the age and pubertal status of the patient populations. The average age of the type 1 diabetic children in the two studies was 11 and 15 years, respectively. Although endothelial dysfunction is present in young children with type 1 diabetes, perhaps the correlations with endothelial function and most cardiovascular risk factors do not become apparent until the mid-teens.

In our study, the average age of the type 1 diabetic children was 12.9 years. The differences in age and pubertal status, in addition to the different methods used to measure endothelial function, could explain differences between various studies. Unfortunately, the age distribution of our study population was too narrow to determine at what age the difference between control subjects and children with type 1 diabetes becomes apparent. Studies with broader age distributions are needed to determine the effects of age and puberty.

Adult and pediatric studies of endothelial dysfunction in diabetic patients have demonstrated significant associations with high LDL, low HDL, hypertension, glycemic control, duration of disease, folic acid status, exercise regimen, and sex (3,5,12,31). Although we did demonstrate that type 1 diabetes was associated with increased arterial stiffness, this study did not find any significant associations with lipids, blood pressure, glycemic control, cytokines, family history, or sex in the children with diabetes. The inability to demonstrate a correlation between established cardiovascular risk factors and increased AI_{75} in children with diabetes is difficult to explain. It is clear that the risk factors measured are, at some point, relevant to the development of atherosclerosis. In children, however, it may be necessary to measure variables that may be more directly related to arterial stiffness such as advanced glycation end products, qualitative lipids, nitrite, and superoxide dismutase.

In control children, we found a significant association between elevated AI and family history of hypercholesterolemia. This may have represented a volunteer bias because the control families who volunteered for the study were more likely to have a positive family history of heart disease. This could explain why the control children had significantly higher triglycerides and blood pressures than the type 1 diabetic subjects. A bias toward increased cardiovascular risk in control subjects would have decreased the difference in AI_{75}, between control subjects and children with diabetes. Nonetheless, type 1 diabetic children demonstrated greater arterial stiffness than control subjects. That higher exercise levels were associated with decreased arterial stiffness in the control subjects but not in the type 1 diabetic subjects suggests that the metabolic derangements of diabetes obscure some of the advantages of exercise.

Despite the novel findings provided by this study, there are several important limitations. The Sphygmocor Vx software used to analyze the wave reflections has not been fully validated in children. The transfer function used to calculate the aortic pressure wave was validated using directly measured aortic and radial pressure waves in adults. Whereas there was a linear relationship between age and AI in the adults, such that the same transfer function could be used at all ages, no childhood data are yet available to confirm the transfer function's validity. Although case-control comparisons eliminated the need for known age-adjusted normal values, the argument could be made that the transfer function may not accurately determine aortic pressure waves in children. In a recent study of adults with type 2 diabetes, Hope et al. (32) suggested that generalized transfer functions may not be valid at all in patients with diabetes. While their concerns about the applicability of transfer functions to specific populations is valid, it should be noted that they found no significant differences between directly measured and transfer function–derived AI in their diabetes population.

The strict matching criteria that were used resulted in a lower than expected total number of matches. With a larger study, associations between AI and lipids, blood pressure, and cytokines might have been uncovered. Another significant weakness of this study was the omission of Tanner staging, which may have resulted in significant pubertal differences between age-matched pairs. Pubertal status may be an important determinant in deciphering when children with type 1 diabetes develop increased arterial stiffness and should be included in all future studies. Finally, the failure to include albuminuria as a study variable is a significant weakness. Several studies have demonstrated the importance of microalbuminuria in predicting atherosclerosis in type 1 diabetic patients (33).

Despite these limitations, the study does provide additional evidence that children with type 1 diabetes have endothelial dysfunction. Further studies are needed to confirm the relationship between arterial stiffness and other modifiable cardiovascular risk factors. Future interventional studies should be developed to provide longitudinal comparisons of optimal blood pressure, lipid, and glucose control with endothelial function in type 1 diabetic children.

In conclusion, the mainstay of type 1 diabetes management must continue to be optimal control of hyperglycemia. While we continue to strive for optimal glucose control in all of our patients, we must also realize that many of our patients simply will not be able to maintain HbA_{1c} concentrations $<7\%$. Furthermore, HbA_{1c} levels well below 7% may be needed to eliminate the diabetes-associated risk of macrovascular disease. It is our responsibility as clinicians to maximize the treatment of all modifiable risk factors to provide our patients with maximal primary prevention. Therefore, the focus must be shifted from risk stratification after coronary events have occurred to the anticipation of cardiovascular disease and the application of safe and effective prevention strategies. Because the risk of recurrent cardiovascular events is higher in type 1 diabetic patients than in nondiabetic patients, current guidelines for treating lipids and blood pressure in children with type 1 diabetes may be underestimating the utility of more aggressive primary prevention. Noninvasive techniques may provide the extra tier of cardiovascular risk stratification information needed to optimize therapy in children with type 1 diabetes.

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