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Vascular and Endothelial Function in Youth with Type 2 Diabetes Mellitus

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Abstract

Purpose of Review—This review aims to discuss the burden of type 2 diabetes in youth and summarize the studies that have utilized noninvasive techniques to assess early vascular disease in youth with type 2 diabetes.

Recent Findings—Noninvasive imaging modalities provide researchers with tools to investigate the vasculature in adolescents with type 2 diabetes. The data published to date consistently show adolescents with type 2 diabetes have greater vascular thickness and stiffness and worse endothelial function compared to their obese and lean peers.

Summary—As the prevalence of type 2 diabetes continues to increase adolescent youth, there is concern adolescents with type 2 diabetes are at risk to develop early onset cardiovascular disease and complications. Future studies need to address treatments that have the potential to improve or reverse vascular dysfunction and decrease the rate of cardiovascular disease and complications.

Keywords

Adolescents; Type 2 diabetes; Vascular; Endothelial function; Carotid artery

Introduction

Type 2 diabetes (T2D) is associated with a 2–4 fold higher risk of developing myocardial infarction, stroke, neuropathy, blindness, and death [1–3]. T2D is also responsible for more cases of renal failure and peripheral vascular disease leading to amputation than any other diseases [4]. Furthermore, there is emerging evidence that T2D is associated with cognitive decline and dementia [5–10]. In 2010, the cost of care for diabetes and its complications in the USA was estimated to be greater than \$316 billion per year and continues to rise [11].

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Compliance with Ethical Standards

Conflict of Interest Amy S. Shah and Elaine M. Urbina declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article contains some unpublished data. All data was obtained after obtained informed consent in accordance with local institutional review board policy.

Prior to 1992, T2D was considered an adult disease. However, in parallel with increases in the rate of childhood obesity, type 2 diabetes has now emerged as a formidable threat to the health of adolescents [12]. T2D accounts for nearly 50% of new diabetes cases in adolescents and the incidence and prevalence continue to rise [13–16]. Data from The SEARCH for Diabetes in Youth study estimates that 20,000 youth currently have T2D [14] but by 2050 this number will quadruple [17]. Similar findings have been seen across the globe in the UK, Japan, and India, where T2D is diagnosed twice as often as type 1 diabetes (T1D) among adolescents [18–20]. As the age of T2D onset has decreased [21], there is a growing concern that complications, traditionally seen in adults, will manifest by early adulthood [22].

A Canadian registry reported that complications, including dialysis, blindness, and amputation occur within 10 years of adolescent T2D diagnosis and youth with T2D are six times more likely to develop cardiovascular disease (compared to peers without T2D) [23••]. Furthermore, rates of complications, including cardiovascular death, are higher in adolescent onset T2D than in T1D despite less severe hyperglycemia, virtually no hypoglycemia, and relatively short disease duration [24, 25]. These findings suggest adolescents with T2D are at accelerated risk to develop target organ damage and many will develop marked comorbidity by early adulthood [26••].

This increased cardiovascular disease risk in youth with T2D has led to the critical need to employ tools that can assess early vascular disease. As a result, well-established noninvasive modalities, previously limited to use in adults [27–31] are now being used in adolescents to detect early vascular changes, reflected by an increase in vessel thickness and stiffness. Below, we describe some of the most widely used imaging modalities in pediatrics and summarize the studies that have been used to assess the effects of T2D on early cardiovascular disease (Table 1).

Carotid Intima Media Thickness

In adults, a higher carotid intima media thickness (IMT) predicts the development of future cardiovascular events, including stroke and myocardial infarction [27–29]. As such, carotid IMT is one of the more powerful tools to assess early atherosclerosis. Carotid IMT is measured using high-resolution B-mode ultrasonography and a high frequency transducer. The far wall intima-media layer of the blood vessel in either the common carotid, internal carotid, or bulb (bifurcation) is imaged and can be quantitated (Fig. 1).

Studies conducted in the USA and Australia demonstrate that adolescents with T2D have higher carotid IMT compared to their obese and lean peers [32–34] with group differences detected as early as 14 years of age [32]. Specifically, data from our center shows that adolescents with type 2 diabetes ($N = 237$) have higher carotid IMT in all segments of the carotid artery (common carotid, internal carotid, and bulb carotid, Fig. 2) compared to lean ($n = 273$) and obese youth ($n = 252$). Risk factors associated with a higher carotid IMT include poorer glucose control (hemoglobin A1c), longer duration of disease, and greater insulin resistance [32]. Shah et al. reported that each 1% increase in hemoglobin A1c or each year increase in duration of T2D was associated with approximately 30% increased odds of

a thicker carotid IMT [35]. Studies also show higher body mass index, higher blood pressure [32], and lower HDL cholesterol levels [36] are associated with a thicker carotid. Longitudinal data have not yet been published, but are expected soon, as our group is concluding a long-term follow-up study. We studied 226 adolescents at baseline and 4.6 years later (initial age 16.6 years, 37% Caucasian and 40% male). Briefly, while IMT appears unchanged in the lean group from baseline to follow-up, there is an increase in carotid IMT for both obese youth and those with T2D, with a slope that is significantly different compared to lean ($p < 0.05$).

Carotid Stiffness

By switching to M mode on the carotid ultrasound image, stiffness of the carotid artery can be assessed. Calculations of carotid stiffness included incremental elastic modulus (Einc) [37], Peterson mean pressure-strain elastic modulus (PEM), Young's elastic modulus (YEM), and beta arterial stiffness index (beta stiffness) [38]. Fewer studies using these measurements have been performed in youth with T2D. Urbina et al. reported higher beta stiffness and YEM in youth with T2D compared to lean youth, but no differences compared to obese controls [33]. PEM and Einc were not reported. Multivariate modeling found higher body mass index and blood pressure were associated with a higher YEM and beta stiffness after adjusting for age, race, and sex [33]. Similar findings have been reported in adults, where higher carotid stiffness has been observed in participants with T2D compared to controls. In adults, greater insulin resistance, hyper-glycemia and triglyceride levels have also been associated with greater carotid stiffness [39, 40].

Arterial Stiffness

In addition to imaging the carotid artery, assessment of peripheral artery mechanics can be helpful in predicting cardiovascular risk [31]. Two commonly used measures of arterial stiffness include pulse wave velocity (PWV) and augmentation index (AIx). PWV is a derived gradient velocity calculated from noninvasive pulse waveforms at two separate peripheral sites (most commonly the carotid and femoral arteries) and the distance between them, where a greater PWV indicates higher arterial stiffness. AIx is derived from pulse waveforms at a single arterial site, calculated as the difference in the augmented and forward waves in an arterial waveform, divided by the overall pulse pressure of the waveform, where a higher AIx is a proxy of greater stiffness. In adults, PWV predicts degree of arterial plaque [41] and future cardiovascular disease mortality and is considered the gold standard measurement of arterial stiffness [42]. Brachial distensibility (BrachD) is another reproducible [43] and validated noninvasive measure of arterial stiffness [30] that has been linked to the development and progression of atherosclerotic vascular disease in adults. BrachD assesses resting vascular function in a medium muscular artery [26••] and is derived from pressure curves generated from arterial pressure signals obtained from a standard blood pressure cuff sphygmomanometer. A lower BrachD indicates increased vascular stiffness.

Only one large study ($n = 670$) has been conducted in youth evaluating arterial stiffness in adolescents with T2D compared to lean and obese controls. Using all three measures described above, Urbina et al. found that adolescents with T2D (mean age 18 years) with

diabetes for less than 4 years had higher PWV and AIX and lower BrachD compared to normal weight and obese youth [44]. In multivariate regression models, obesity was an independent predictor of PWV and BrachD (but not AIX) after adjustment for risk factors [44]. Further work from the same group showed that both PWV and AIX are higher in non-Hispanic Black compared to non-Hispanic White youth with T2D [45], and lower BrachD is evident in the vasculature before the onset of T2D diabetes, specifically in youth with pre-diabetes [46]. Recently, Li et al. showed that inflammation may also be a risk factor for increased arterial stiffness. Their group compared arterial stiffness in adolescents with recent onset T2D. Compared to those with no inflammation, those with low grade inflammation, defined as a high-sensitivity C-reactive concentration of >2 mg/dL, had a higher PWV, AIX and lower BrachD. Furthermore, C-reactive protein concentration was an independent determinant of each of the arterial stiffness measurements [47].

Endothelial Function

Alteration in the vascular endothelium is another means to assess the health of the arteries. Flow mediated dilation (FMD) has been used most commonly in adolescent studies [48, 49]. As currently measured, the brachial artery is briefly occluded by a pneumatic cuff and released. Dilation of the distal artery normally occurs and the resultant increased blood flow and diameter are assessed by ultrasound [50]. The percent change in flow after ischemic stress is called FMD. The brachial artery typically dilates 6–12% in healthy people [48, 49] and diminution of the response is termed endothelial dysfunction. Endothelial dysfunction is associated with the cardiovascular disease risk factors and coronary artery atherosclerosis in adults [51].

Only recently have the results of two endothelial function studies in youth with T2D been published. Naylor et al. reported that adolescents with T2D have lower brachial FMD compared to normal weight (but not obese) controls [34]. Ohsugi et al. found that adolescents with T2D have lower brachial FMD than youth with T1D [52]. Lower BrachD in the T2D group occurred despite both groups having similar hemoglobin A1c levels and youth with T2D having a shorter diabetes duration [52]. These initial findings suggest that obesity and/or insulin resistance may be an important risk factor associated with endothelial dysfunction. Indeed, several studies have also shown overweight and obese children with insulin resistance show reduced FMD compared with control subjects when matched for blood pressure, cholesterol, and glucose levels [53].

Endothelial function can also be assessed by peripheral arterial tonometry (Endo-PAT) where probes are placed on one finger of each hand (one finger is the test, the other is the control) and pulsatile signals are recorded. A blood pressure cuff is then inflated to occlude blood flow and the response after deflation is recorded as the reactive hyperemia index, which correlates with the coronary blood flow response to acetylcholine at cardiac catheterization [54]. In unpublished work from our center, we evaluated endothelial function using Endo-PAT in 379 adolescents and young adults (mean age 23 years) who were lean, obese, or had T2D. We found no differences by group but observed an inverse correlation between A1c and reactive hyperemia index. This finding was confirmed using laser flow Doppler in this same group of adolescents. Laser flow Doppler uses a probe placed on the

finger to assess endothelial function or microvascular perfusion. Similar to above, after release of a blood pressure cuff, post occlusion reactive hyperemia (PORH) is measured. The baseline perfusion is subtracted from the peak perfusion and is expressed as a percent. At our center, we observed an inverse association between A1c and PORH in lean, obese, and T2D youth. These findings suggest that glucose control may be important for endothelial function, at least in young adults.

There are emerging data suggesting that endothelial function can improve in youth with T2D. Eight youth with T2D participated in a supervised exercise training program for 12 weeks. Youth who exercised had improvement in brachial FMD compared to five youth with no exercise [55•]. These changes occurred without significant changes in BMI, suggesting that physical activity, even without weight loss, may improve vascular health in adolescents with T2D. Additional larger scale studies are needed to confirm these results.

Gaps and Limitations

Despite the wide use of noninvasive imaging modalities in the pediatric research setting, there are limitations of the methods that should be discussed. First, except for a few small pediatric validation studies of PWV [56], AIx [57], and endothelial function measured by Endo-PAT [54], none of the remaining imaging modalities have been validated specifically in this age group. However, there is no reason to believe that the experiments proving that simultaneous noninvasive measurements correlated with intra-arterial measurements in adults would not apply equally to children, particularly those who are essentially of adult size [31, 58]. Second, there is lack of normative data by age, race, and sex. While several studies have included data on larger numbers of healthy youth, nicely reviewed here [59••], there is lack of consistency among techniques so the “normal” values must be interpreted only for the specific device used. Finally, large-scale longitudinal and intervention studies have not been reported yet, therefore it is unclear how carotid and arterial thickness and stiffness progress overtime and whether lifestyle or T2D treatments have the potential to improve or reverse thickness and stiffness and, eventually, decrease the rate of cardiovascular disease and complications.

Conclusions

Noninvasive imaging modalities have provided researchers with tools to investigate the vasculature in high risk populations, with the data to date consistently showing that youth with T2D have greater vascular thickness and stiffness compared to their peers. While there is insufficient evidence at this time to recommend the use of any of these methods in routine clinical care, there are sufficient data to show these tools provide valuable information and can be used reliably when utilized in youth with T2D.

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Fig. 1.

a Ultrasound image taken from the carotid artery demonstrating the intima-medial layer. The intima-media thickness is measured (in mm) from the border between the echolucent vessel lumen and the echogenic intima (*white arrow*) and the border between the echolucent media and echogenic adventitia (*red arrow*). Also shown is Meyer's arc device can be used to record angle of insonation when measuring carotid intima-media thickness measurements.

b Horizontal 2-D image of carotid artery with the M mode cursor placed in the common carotid. Minimal and maximal artery diameters are measured to calculate carotid stiffness

Fig. 2.

Mean carotid intima media thickness in the common carotid, bulb, and internal carotid arteries from lean ($n = 273$), obese ($n = 252$), and adolescents with type 2 diabetes ($n = 237$) studied in Cincinnati, Ohio. Mean age 18 years, 41% white, 35% male. Values shown in millimeters where * indicates T2D > lean and obese at $p < 0.05$; ** indicates T2D > obese > lean at $p < 0.05$

Table 1

Noninvasive imaging methods

Technique	Method	Device	Variable unit	What does it measure?	Studies in youth with type 2 diabetes
Carotid thickness					
Carotid intima Media thickness	B mode ultrasound	Ultrasound with linear array transducer	mm	Thickness of the intima media layer of the carotid artery either in the common carotid, bulb carotid, or internal carotid	Ref. [32–36]
Carotid stiffness					
Young's elastic modulus, Beta stiffness index	M mode Ultrasound	Ultrasound with linear array transducer	YEM (mm Hg/mm); beta (unitless)	Stiffness in the carotid artery	Ref. [33]
Arterial stiffness					
Brachial distensibility	Oscillometric systolic/diastolic blood pressure	Pulsemetric DynaPulse	% change/mmHg	Resting distensibility of the medium muscular artery in the arm. Lower is worse	Ref. [44, 47]
Pulse wave velocity	Applanation tonometry	AtCor SphygmoCor	m/s	Speed of pulse wave along an arterial segment	Ref. [44, 47]
Augmentation index	Applanation tonometry	AtCor SphygmoCor	%	Increase in central systolic pressure due to reflected wave as a percentage of central pulse pressure	Ref. [44, 47]
Endothelial function					
Brachial artery flow mediated dilation	Ultrasound	Ultrasound	FMD max (%)	FMD max is maximum % change at any time period post occlusion (30 to 120 s)	Ref. [34, 52, 55•]
Peripheral arterial tonometry	EndoPat	Itamar	%	Increase in blood flow in the digit after release of occlusion normalized to the control finger	No published studies
Microvascular endothelial function	Laser Doppler	Perimed	Perfusion units	Change in perfusion units after heating	No published studies