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Children with Type 1 Diabetes Have Delayed Flow-Mediated Dilation

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ABSTRACT

Objectives: Children with type 1 diabetes have accelerated atherosclerosis with early endothelial dysfunction as measured by reduced flow-mediated dilation (FMD) at 60 seconds postischemic stress (early FMD). Delayed dilation may also occur in the presence of cardiovascular risk factors and may be a more sensitive marker. No data exist that evaluate FMD beyond 60 seconds (delayed FMD) in children with type 1 diabetes. We aimed to compare early and delayed FMD in children with type 1 diabetes and in healthy children.
Methods: We studied 66 children 13.5±2.8 years of age; 29 were males. Of the 66 children, 38 had type 1 diabetes, and 28 were healthy age- and gender-matched controls. Evaluation of brachial artery FMD was performed at 60 seconds (FMD_{60s}) and 120 seconds (FMD_{120s}) postischemic stress. Early FMD was defined as peak FMD_{60s} and delayed FMD as peak FMD_{120s}.
Results: Children with type 1 diabetes had diabetes durations of 5.4±4.6 years and median glycated hemoglobin levels of 8.8 (6.6 to 14)% (73 [49 to 130] mmol/mol). Of the children, 8 with type 1 diabetes and 1 healthy child had delayed FMD; a relationship was seen between the prevalence of early FMD and delayed FMD in children with type 1 diabetes and healthy children, respectively (p=0.019). Children with type 1 diabetes and delayed FMD had lower FMD_{60s} than children without delayed FMD (2.50±3.61 vs. 6.14±3.83 percentage units; p=0.02). Children with type 1 diabetes had lower FMD_{60s} than healthy children (5.38±4.0 percentage units; p=0.03) but not FMD_{120s} (7.56±3.5 percentage units; p=0.47).
Conclusions: Delayed FMD patterns occur in children with type 1 diabetes and detect children who have more severe vascular abnormalities. The standard FMD_{60s} remains the better marker to identify children at increased risk for cardiovascular disease.

Mots clés :
enfants
dilatation induite par le flux
diabète de type 1

RÉSUMÉ

Objectifs : Les enfants atteints du diabète de type 1 montrent une accélération de l'athérosclérose associée à un dysfonctionnement endothélial précoce déterminé par la diminution de la dilatation induite par le flux (DIF) 60 secondes après un stress ischémique (DIF précoce). La dilatation retardée peut aussi apparaître en présence de facteurs de risque cardiovasculaire et être un marqueur plus sensible. Aucune donnée n'a évalué la DIF au-delà de 60 secondes (DIF retardée) chez les enfants atteints de diabète de type 1. Notre objectif était de comparer la DIF précoce et la DIF retardée chez les enfants atteints du diabète de type 1 et les enfants en bonne santé.
Méthodes : Notre étude portait sur 66 enfants de 13,5±2,8 ans, dont 29 étaient des garçons. Parmi les 66 enfants, 38 souffraient du diabète de type 1 et 28 étaient des témoins en bonne santé appariés selon l'âge et le sexe. L'évaluation de la DIF dans l'artère brachiale était réalisée 60 secondes (DIF_{60s}) et 120 secondes (DIF_{120s}) après le stress ischémique. La DIF précoce était définie par la FMD_{60s} maximale et la DIF retardée, par la DIF_{120s}.

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Résultats : Les enfants étaient atteints du diabète de type 1 depuis 5,4±4,6 ans et avaient des concentrations médianes d'hémoglobine glyquée de 8,8 (de 6,6 à 14) % (73 [de 49 à 130] mmol/mol). Parmi les enfants, 8 enfants atteints du diabète de type 1 et 1 enfant en bonne santé avaient une DIF retardée ; on observait un lien, et ce de manière respective, entre la prévalence de la DIF précoce et la DIF retardée chez les enfants atteints du diabète de type 1 et les enfants en bonne santé (p=0,019). Les enfants atteints du diabète de type 1qui avaient une DIF retardée avaient une DIF_{60s} inférieure aux enfants sans DIF retardée (2,50±3,61 *vs* 6,14±3,83 points de pourcentage; p=0,02). Les enfants atteints du diabète de type 1 avaient une DIF_{60s} inférieure aux enfants en bonne santé (5,38±4,0 points de pourcentage; p=0,03), mais non de la DIF_{120s} (7,56±3,5 points de pourcentage; p=0,47).
Conclusions : Les profils de DIF retardée apparaissent chez les enfants atteints du diabète de type 1 et permettent de détecter les enfants qui ont des anomalies vasculaires plus graves. La DIF_{60s} reste le meilleur marqueur pour déceler les enfants ayant un risque accru de maladie cardiovasculaire.

Introduction

The leading cause of mortality in type 1 diabetes is cardiovascular disease (1). Vascular endothelial dysfunction is an early and fundamental event in the development of the atherosclerosis (2) that precedes the development of vascular complications in diabetes (3).

Vascular endothelial dysfunction can be evaluated by ultrasound assessment of the brachial artery diameter before and after ischemic stress caused by sphygmomanometer cuff inflation (4,5). This is known as flow-mediated dilation (FMD). Healthy arteries release endothelium-derived nitric oxide and dilate in response to ischemic stress (6); however, if endothelial dysfunction is present, this vasodilatory response (FMD) is reduced, delayed or absent (7). Abnormal FMD of the brachial artery relates to the extent of angiographically detectable coronary artery disease (8) and correlates with future cardiovascular events in adults with established and asymptomatic cardiovascular disease (9–14). FMD is usually assessed around 60 seconds after cuff deflation (5) or area under the curve for a given time period (15,16). Measuring FMD at 60 seconds postischemic stress can miss later arterial dilation in response to ischemic stress (16,17). Extending the measurement duration may allow a more sensitive assessment of vascular dysfunction and assessment of peak FMD. Moreover, assessment of FMD at 120 seconds postischemic stress has identified a delayed FMD pattern in adults with type 2 diabetes (18).

Children with type 1 diabetes have reduced FMD at 60 seconds postischemic stress relative to healthy age-matched children (19,20). No studies have assessed delayed FMD patterns (i.e. peak FMD at 120 seconds) in children with type 1 diabetes. Therefore, we aimed to evaluate FMD at 60 seconds and 120 seconds postischemic stress in children with type 1 diabetes compared to healthy children. We hypothesized that children with type 1 diabetes would have delayed FMD patterns when compared to those of healthy children, which would be a more sensitive marker than early FMD.

Methods

Subjects and study design

Sixty-six children (8 to 18 years of age; 29 males) participated in the study, including 38 children with type 1 diabetes and 28 age- and gender-matched healthy children. Children with type 1 diabetes were recruited from pediatric clinics at Women's and Children's Hospital and Flinders Medical Centre, South Australia, and were evaluated at baseline in a randomized controlled trial (21). Inclusion criteria were diagnosis of type 1 diabetes with duration greater than 1 year, being between 8 and 18 years of age, having insulin requirements greater than 0.5 units/kg/day and body mass indexes (BMIs) greater than the 50th percentile for age and sex. Exclusion criteria included severe hypoglycemia episodes; recurrent diabetic ketoacidosis; other serious comorbidities, not including being treated for hypothyroidism or celiac disease; and children who were already being treated with metformin, statins, antihypertensives or multivitamins. Healthy children were recruited from siblings or friends of the children with type 1 diabetes and relatives of staff members.

The study was approved by the Women's and Children's Hospital and Flinders Medical Centre Human Research Ethics Committees (HREC 2327/12/13 and HREC 433.12), which were the recruitment sites. All children were evaluated at Women's and Children's Hospital. Written informed consent was obtained from the parents/guardians of the children and from the children themselves if they were older than 16 years.

Physical examination and laboratory methods

Weights and body compositions were measured while they were wearing light clothing by using a BC-418 segmental body composition analyzer (Tanita, Tokyo, Japan, distributed by Wedderburn, Inglewood, NSW, Australia). Heights were measured using a wall-mounted stadiometer. BMI *z* scores were calculated using 3.2 EpiInfo database v. 2 and Centers for Disease Control and Prevention 2000 standardized reference charts (https://www.cdc.gov/epiinfo/index.html). Blood pressures were measured using DINAMAP (Carescape V100 Vital signs monitor, GE Healthcare, Milwaukee, Wisconsin, United States) with an appropriately sized cuff on the left arm after 10 minutes of rest in the supine position. The mean of 3 consecutive measurements was recorded. Pubertal development was assessed by self-reports using the Tanner stage illustration and was categorized as prepuberty (Tanner 1), midpuberty (Tanner 2 and 3) or late puberty (Tanner 4 and 5).

Cholesterol (total, high-density lipoprotein [HDL] and low-density lipoprotein [LDL]) levels were measured by using commercial enzymatic assays on Roche/Hitachi cobas C systems. Glycated hemoglobin (A1C) levels were measured using a latex immunoagglutination inhibition methodology (DCA 2000 Hemoglobin A1c Reagent Kit; Bayer, Toronto, Ontario, Canada).

Ultrasound assessment of vascular endothelial function (FMD)

An experienced pediatric sonographer (RG) performed ultrasound assessments of FMD using high-resolution B-mode ultrasound examinations with a 17 to 5 MHz linear array transducer (iU22; Philips, Bothell, Washington, United States) as described previously (19,21,22). In brief, the brachial artery of the right arm was visualized and scanned in a longitudinal section 2 to 15 cm above the elbow. The brachial artery's internal diameter, defined as the distance between the artery's intima boundaries, was measured at baseline, at 60 seconds ±15 seconds and 120 seconds ±15 seconds postischemic stress. Ischemic stress was obtained using a sphygmomanometer placed on the distal forearm and inflated to a systolic pressure of 250 mm Hg for 4 minutes. Then 4 internal diameter measurements,