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Early changes of arterial elasticity in Type 1 diabetes with microvascular complications - A cross-sectional study from childhood to adulthood

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ABSTRACT

Aim: To examine the trajectory of small artery elasticity (SAE) and pulse pressure (PP) in people with Type 1 diabetes and non-diabetic controls across the lifespan, and explore associations with microvascular complications (CX+).
Methods: This cross-sectional study included 477 Type 1 diabetes patients (188 with CX+, 289 without CX−) and 515 controls. Relationships between SAE and PP and age were evaluated using segmented linear regression. Logistic regression was used to assess the associations between microvascular complications (retinopathy and/or nephropathy) and SAE and PP.
Results: SAE peaked significantly later among controls than diabetic patients CX− vs. CX+ (21.2 vs. 20.4 vs. 17.6 years respectively, $p < 0.001$). In adults, mean SAE was significantly lower in CX+ vs. CX− vs. controls (6.8 vs. 7.8 vs. 8.0 ml/mm Hg × 10; $p < 0.0001$), and mean PP was significantly higher in CX+ vs CX− and controls (60 vs. 55 vs. 53 mm Hg; $p < 0.0001$).
Conclusion: Type 1 diabetes CX+ subjects have an earlier peak and decline in SAE relative to CX− and controls, who did not differ. Lower SAE and higher PP were associated with increased odds of Type 1 diabetes complications in adults. These clinically applicable techniques demonstrate an association between accelerated vascular aging and vascular complications in diabetes.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of mortality for Type 1 diabetes patients globally. CVD originates early in childhood and its progression is related to chronic exposure to risk factors and vascular aging. Type 1 diabetes is a major risk factor for CVD, however exposure to hyperglycemia from early life and its impact on long-term vascular outcomes in adulthood are not well-understood. CVD in adulthood is intimately linked with diabetic microvascular complications and endothelial dysfunction as evidenced by the strong association between nephropathy, retinopathy and macrovascular events.[1–4] This is likely mediated through a systemic endotheliopathy, with a long period, often decades of subclinical vascular dysfunction and damage prior to clinically evident vascular events, which usually occur in middle to older age. Non-invasive assessments of functional and structural vascular health would be useful clinically and as surrogate end-points in clinical trials.

Pulse pressure (PP) can be derived from routine blood pressure measurements, while both small artery elasticity (SAE) and PP can be measured non-invasively by pulse wave analysis (PWA). SAE has been used in a cross-sectional study to describe the natural history of arterial health across the lifespan in persons without diabetes.[5] There are age-dependent changes in vascular elasticity, with a clear increase in SAE during childhood, reaching "peak elasticity" between the second and third decades of life. A subsequent and gradual

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decrease in elasticity, or "stiffening", is observed through adult life. Obesity and Type 2 diabetes during childhood precipitate a premature increase in SAE,[6] likely representing accelerated vascular aging; with a postulated subsequent premature decrease in elasticity during adulthood.[7,8] However, to our knowledge no studies to describe such phenomenon have been performed in Type 1 diabetes patients across the lifespan. SAE correlates with measures of inflammation,[9] endothelial function[10,11] and measures of vascular function including augmentation index measured by systolic PWA.[12] The Multi-Ethnic Study of Atherosclerosis, a large population based study, demonstrated an association between lower SAE and incident CVD in older adults.[13] Wider PP is an index of arterial stiffness and an independent predictor of CVD and mortality.[14,15]

The association between SAE, PP and microvascular complications through the lifespan has not been explored in Type 1 diabetes. Hence this study aimed to describe the natural history of vascular elasticity (SAE, PP) across the life-span in patients with Type 1 diabetes and subjects without diabetes; and to explore associations with microvascular complications.

2. Methods

This cross-sectional study was approved by the Human Research Ethics Committees of the Children's Hospital at Westmead, Sydney, Australia and St Vincent's Hospital, Melbourne, Australia. Written informed consent was obtained from all participants and/or their legal guardians.

2.1. Study subjects

Participants were 992 children, adolescents and adults, including 477 with Type 1 diabetes and 515 controls without diabetes. Participants were recruited through the Diabetes Complications Assessment Centre at the Children's Hospital at Westmead, Sydney and diabetes outpatient clinics at St Vincent's Hospital, Melbourne. Recruitment was not restricted by subject age, nor was there a cap on recruitment for any particular age category. Every non-pregnant patient attending the diabetes clinics was offered study participation, and over 90% of those asked agreed to participate. Non-diabetic control subjects were recruited from a convenience cohort through a school population based study and visitors to the hospital, and adult controls were recruited through a research volunteer registry including patient family members or friends and people from the local community. Height was measured to the nearest 0.1 cm using a standard stadiometer and weight measured to the nearest 0.1 kg using a digital scale and BMI calculated. Obesity was defined as per the International Obesity Task Force (IOTF).[16]

2.2. Definitions of microvascular complications

As our study included patients from both pediatric and adult hospitals with a wide range of age and diabetes duration as well as severity of complications, patients were classified into a binary outcome group as being free from diabetes microvascular complications (CX−) or having microvascular complications (CX+). CX+ included at least one of diabetic retinopathy[9] and/or diabetic nephropathy[5] end-point, with definitions relevant to these cohorts,[17,18] as described below. Using both retinopathy and renal definitions as below, of the 477 Type 1 diabetes participants, 294 subjects were free of microvascular and macrovascular complications (CX− group) and 183 had microvascular complications (CX+ group). Key SAE and PP outcome analyses were also repeated using two alternate definitions of complications described below.

In children and adolescents, diabetic retinopathy (DR) was defined as at least one microaneurysm/hemorrhage in either eye assessed according to the early treatment of Diabetic Retinopathy Study (ETDRS) adaptation of the modified Airlie house classification (level 21, non-proliferative diabetic retinopathy (NPDR) or greater).[19] In adults, retinopathy was defined as clinically significant proliferative retinopathy (PDR) or retinopathy requiring laser treatment.

In children and adolescents, diabetic nephropathy (DN) was defined by either: an albumin excretion rate (AER) >7.5 μg/min from three overnight, timed urine collections or estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 (see below). This AER cutoff is above the 95th percentile of the normal adolescent population, which has been shown predictive of albuminuria.[20,21] In adults the cut-off for albuminuria was >15 μg/min in at least two of three 12 or 24-hour urine collections. eGFR was calculated: in children and adolescents (<18 years old) using Schwartz equation[22] and in adults (≥18 years old) using CKD-EPI formula.[23]

Two alternate criteria for complication categorization were also analysed (see Supplementary material): a) complications were by age related retinopathy criteria and/or nephropathy based on AER and eGFR < 90 ml/min/1.73 m^2; and (b) only renal status (AER and eGFR < 60 ml/min/1.73 m^2) was considered. DR status was not considered at all.

2.3. Arterial elasticity

SAE and PP were measured in triplicate using diastolic pulse-wave analysis (PulseWave™ CR-2000, Hypertension Diagnostics, Eagan, MN). The CR-2000 software uses a modified Windkessel third order differential equation to calculate SAE. Following 5–10 min of supine rest, an appropriately sized upper arm blood pressure cuff was placed on the left arm. An ergonomically padded splint (wrist stabilizer) was applied to the right wrist in order to minimize movement of the tonometric sensor placed over the right radial artery (Arterial PulseWave™ Sensor). Once optimal waveforms and a stable baseline were achieved, arterial waveforms were recorded for 30 s and then digitized at 200 samples/s and stored by the device.

Systolic and diastolic blood pressure (SBP, DBP) and PP were measured using an appropriately sized cuff with a calibrated automated sphygmomanometer incorporated in the HDI-PulseWave analysis instrument (PulseWave™ CR-2000, Hypertension Diagnostics, Eagan, MN). PP was defined as the difference between resting SBP and DBP. The mean of three replicates for each participant was used for data analyses.

2.4. Biochemical analyses

Venous blood was taken for measurement of glucose, HbA1c, lipids (total cholesterol, HDL-cholesterol and triglycerides) using routine chemical pathology. LDL-cholesterol was calculated using the Friedewald equation. Adults were fasted, whereas children and adolescents had variable fasting status.

2.5. Statistical analysis

In view of the known increase in SAE measures during early life and subsequent gradual decline during adulthood, segmented linear regression was used to evaluate potential break-points (thresholds) in the relationship between age and vascular health parameters (SAE, PP). The break-point was determined at the point where the slope of the linear relationship changed, using the least squares method to minimize the sum of squared differences. We also tested whether the slopes of the relationships between age and PWA parameters were significantly different above and below the threshold.

Descriptive statistics are reported as mean + standard error (SEM). Thresholds of age values obtained from the above estimation separately for SAE and PP were compared using *t*-test. One-way

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