Journal of Pediatric Endocrinology

Open Access

Austin Publishing Group

Original Article

Endothelial Dysfunction and Diabetes Related Complications in Adolescents with Type 1 Diabetes

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Received: August 04, 2021; **Accepted:** September 02, 2021; **Published:** September 09, 2021

Abstract

Introduction: Patients with Type 1 Diabetes (T1D) are at high risk of developing vascular complications. Endothelial Dysfunction (ED) is the early reversible stage of vascular disease.

Aim: Poor Diabetic control is associated with ED. Based on a hypothesis we aimed to determine the relationship between metabolic control and endothelial function in a cohort of adolescents with T1D.

Methods: 42 adolescents with T1D were recruited. Weights, heights and BMI were recorded. Blood pressure was measured, followed by assessment of Reactive hyperaemia index (RHI) by Endo-PAT. Fasting blood samples were taken for evaluation of HbA1c, liver, renal function, lipid profile. Inflammatory markers (adiponectin, leptin, thrombomodulin, serum Intravascular Adhesion Molecules (sICAM), E-Selectin and p-Selectin) were measured in 20 patients. Urinary microalbumin to creatinine ratio measured. Participants completed a physical activity questionnaire. Baseline data included the date of diagnosis, duration of diabetes, current insulin dose, insulin regimen, daily screen time and relevant family history of early cardiovascular disease.

Results: Reactive hyperaemia index correlated with age. Thirteen adolescents (31%) had low RHI, suggesting relatively impaired endothelial function. Lower RHI correlated with higher diastolic blood pressure (r=-0.34) and p-Selectin level (r=-0.3) suggesting impairment in vascular health. Poor metabolic control was associated with impaired lipid profile (r=0.55), higher diastolic blood pressure (r=0.38) and higher level of inflammatory markers P-selectin (r=0.55). Active life style was associated with improved blood pressure (r=-0.35) and lipid profile (r=-0.39).

Conclusion: RHI did not correlate with HbA1c. RHI correlated with Diastolic blood pressure and P- selectin.

Keywords: Endothelial dysfunction; Type 1 Diabetes; Adolescents

Introduction

Type 1 Diabetes (T1D) occurs with increasing frequency worldwide [1]. It is an important risk factor for the development of cardiovascular disease. Though atherosclerosis, Myocardial Infarction (MI) and Cerebrovascular Disease (CVD) develops later in life, endothelial dysfunction, which is the early reversible stage of vascular disease, begins in childhood [2-5]. Individuals with good glycaemic control have a two-fold increased incidence of cardiovascular disease while those with poor control have a ten-fold increased risk compared to general population [6].

Endothelial function is affected by many factors such as hyperglycaemia which induces a low grade vascular inflammatory state that impairs the homeostasis of the endothelium leading to release of various inflammatory cytokines and inappropriate release of vasoactive materials leading to endothelial dysfunction and to the development of early atherosclerosis [3,7]. Some studies on patients with T1D showed that hypoglycaemia and fluctuations in glucose levels causes oxidative stress, which leads to endothelial dysfunction [8-10]. Markers of inflammation (E-Selectin, p-Selectin, serum intercellular adhesion molecules (sICAM) and thrombomodulin) have been linked to endothelial dysfunction in many studies [7,11-16].

Dyslipidaemia is a known risk factor for the development of atherosclerosis. Studies show a high prevalence of hyperlipidaemia in adolescents with T1D and an association with poor glycaemic control [17,18]. Obesity in adolescence is a global health issue, which leads to endothelial dysfunction through associated hyperlipidaemia, hypertension, increased oxidative stress and insulin resistance [17,19-21]. Leptin and adiponectin are adipokines, secreted by adipose tissue, which play a role in lipid and carbohydrate metabolism, insulin sensitivity and inflammation [22]. In patients with obesity, higher adiponectin is associated with vascular complications [23].

Hypertension contributes greatly to cardiovascular disease; even a family history of hypertension could impair endothelial function [24,25]. Studies show that adolescents with T1D and hypertension have higher markers of inflammation indicating impaired endothelial

Citation: Metwally N, Macken AP, McDonnell C, O'Gorman CS, Molloy EJ and Roche EF. Endothelial Dysfunction and Diabetes Related Complications in Adolescents with Type 1 Diabetes. J Pediatri Endocrinol. 2021; 6(2): 1045.

function [26-28].

Persistent microalbuminuria is the first stage in diabetic renal disease, which can progress to end stage renal failure [29,30]. Higher albumin to creatinine ratio in the urine was found to be associated with endothelial dysfunction in adolescents with T1D [31,32]. Smoking, either active or passive induces oxidative stress leading to endothelial dysfunction [33,34]. Some recent studies showed a link between endothelial function and psychological disorders where depression and hopelessness were linked to endothelial dysfunction [35,36].

Diet has a remarkable effect on vascular health many nutrients like fish oil, L-Arginine, antioxidants, folic acid and vitamin D have cardio protective effect [37]. Sedentary lifestyle and consumption of high fat diet is associated with endothelial dysfunction [38,39]. Exercise improves insulin sensitivity, glycaemic control, blood pressure and endothelial function [33-35].

Endothelial function can be assessed invasively during cardiac catheterization through acetylcholine infusion [40]. Non-invasive methods of evaluating endothelial function include flow mediated dilation, intimal medial thickness measurement and peripheral arterial tonometry. Endothelial function can be evaluated by assessing different biomarkers of endothelial dysfunction such as; endothelial progenitor cells, circulating angiogenic cells and endothelial micro particles and through evaluating markers of inflammation like E-Selectin, p-Selectin, intravascular adhesion molecules, and adiponectin [41,42].

We hypothesized that Endothelial dysfunction measured by reactive hyperaemia index is associated with worse glycaemic and metabolic control in adolescents with T1D. Based on this hypothesis we sought to determine the relationship between endothelial function and metabolic control in a cohort of adolescents with Type 1 diabetes attending the Paediatric diabetes and endocrinology service at a tertiary university teaching hospital. Thus, identifying those at increased risk of cardiovascular disease and enabling targeted intervention to reduce microvascular and macrovascular complications of T1D.

Methods

Forty-two patients attending Paediatric Diabetes and endocrinology service at Tallaght Hospital were recruited to the study following informed consent. Participants aged 12 to 19 years, with at least 2 years duration of Diabetes. Exclusion criteria included pregnancy and current/previous smoking. Ethical approval was granted by the Tallaght University Hospital (TUH)/St. James' Hospital (SJH) Joint Research Ethics Committee (REC). Baseline data were collected including duration of diabetes, insulin regimen, dose and method of administration, weekly screen time, family history of early onset coronary heart disease (defined as Myocardial Infarction (MI)/Cerebrovascular Accident (CVA) before the age of 55 years in a 1st degree relative), dyslipidaemia and hypertension.

Physical activity was assessed using Physical Activity Questionnaire for Adolescents (PAQ-A) [43]. This questionnaire was designed for use by adolescents during the school year and is not suitable to be used during holidays. It is a 7-day recall questionnaire, consisting of 8 items, Item 1 represent spare time activity, item 2 to 7 represents physical education at school, afternoon activity, weekend activities, item 8 takes the mean of the whole week activity. For each item of the questionnaire, the scores range from 1 to 5. The overall summary score is obtained by calculating the mean for all 8 items of the questionnaire and the final mark was out of 5 [43]. On the day of the study patients arrived fasting from midnight for at least 8 hours with no caffeine for 24 hours.

Anthropometric measures (weight, height and BMI) were obtained. Reactive Hyperaemia Peripheral Artery Tonometry (RH-PAT) was assessed in all candidates using the Endo-PAT testing a validated test for endothelial function in adolescents [44].

The Endo-PAT device (Itamar Medical Ltd., Caesarea, Israel) was used in our study. In the assessment, patients lay down on a bed with their hands at heart level in a comfortable position such that the fingers were hanging freely. Fingertip probes were placed on both index fingers and pulse wave amplitudes recorded for the duration of the study, baseline measurement was obtained for 5 minutes, arterial flow to the non-dominant arm was occluded for 5 minutes by inflating a blood pressure cuff to 40mmHg above the systolic pressure (measured initially in the control arm) then the cuff was rapidly deflated to allow for reactive hyperaemia. An integrated software program compared the pulse wave amplitude in the two fingers before and after the occlusion to calculate the RH-PAT score (reactive hyperaemia index score). The RH-PAT score was calculated as the ratio of the average pulse wave amplitude measured over 60 seconds, starting 1 minute after cuff deflation to the average pulse wave amplitude measured at baseline. This ratio was normalized to the concurrent signal from the contralateral finger to correct for changes in systemic vascular tone [45].

Blood samples were obtained following RH-PAT assessment for glycosylated haemoglobin (HBa1c), lipid profile (Triglycerides (TG), High Density Lipoproteins (HDL), Low Density Lipoproteins (LDL)), urea and creatinine, liver function tests (ALT, Alkaline Phosphatase and GGT), thyroid function tests (Thyroid Stimulating Hormone (TSH), free Thyroxine (T4) and Thyroid Peroxidise Antibodies (TPO)) and serum tissue transglutaminase antibody testing were measured.

In 21 patients (50%) adiponectin, leptin, thrombomodulin, E-selectin, p-Selectin and Serum Intercellular Adhesion Molecules (SICAM) were also measured. A first morning urine sample for microalbumin to creatinine ratio was collected.

Data were analysed using SPSS software. Z-Score for Height were calculated using the Clinical growth standard for Irish children [46]. BMI Z-Scores were calculated using body mass index reference curves for UK [47]. Blood pressure percentiles and z-scores were calculated using normative blood pressure data for age and sex for Children and Adolescents from the American Heart Association [48]; American centiles for blood pressure were used as there are no similar population level BP data in populations of Irish children.

Statistical analyses included Chi Squared statistics and independent samples t-test were used as appropriate for group comparisons (males *vs.* females, patients with family history of cardiovascular disease Vs Patients with no family history of same, patients using multiple daily injections *vs.* patients using CSII), correlations were assessed using

Pearson correlation coefficient. Based on the sample size in this study.

Results

One hundred and sixty-five patients fulfilling the study criteria attended the service regularly with 15 patients declined participating in the study due to school commitments or personal reasons. Forty-two patients participated with their ages ranging between 12.29 and 18.44 years. 23 females (54.7%) and 19 males (45.2%). The time since diagnosis of T1D ranged between 2 years and 12 years (Table 1). 22 patients (52.38%) were on continuous subcutaneous insulin infusion (CSII), 16 patients (38.1%) were on multiple daily injections of insulin regimen (MDI), 3 patients on twice daily premixed insulin (7.14%) and one patient was on twice daily premixed insulin and evening long acting insulin (2.38%).

In our study population, those on Continuous Subcutaneous Insulin Infusion (CSII) were significantly younger at diagnosis (p=0.001). There was no significant difference in Reactive hyperaemia index (RHI) or HBA1c between patients on Multiple Daily Injections of insulin (MDI) and patients on CSII. Eight candidates had BMI above 25Kg/m^2 (BMI SDS between 1.3 and 3.57), including 6 who were overweight (BMI 25-30 kg/m^2), and 2/8 who were obese (BMI >30kg/m^2). A family history of early onset cardiovascular disease was positive in 21 candidates (50%). There was no statistically significant difference in RHI, BP, glycaemic control or lipid profile between the group of patients with family history of cardiovascular disease and patients with no family history of same HbA1c showed strong positive correlation with Low Density Lipoprotein (LDL) (r=0.55), Triglycerides (TG) (r=0.6), BMI (r=0.37) and DBP (r=0.38), the total daily dose of insulin (r=0.32), screen time (r=0.31), thrombomodulin (r=0.31), SICAM (r=0.28), adiponectin (r=0.33), p-Selectin (r=0.55) and weakly negative correlation with PAQ (r=-0.23) (Table 2).

RHI values below 1.67 suggesting endothelial dysfunction were found in 13 patients [44,49]. The group with lower RHI were significantly younger than the group with higher RHI (p=0.005). There was weak negative correlation between RHI and duration of Diabetes (r=-0.24) and positive correlation with the age at diagnosis (r=0.4). RHI correlated negatively with Diastolic blood pressure (r=-0.34) and p-Selectin level (r=- 0.3). RHI had a weak positive correlation with the PAQ-A score (r=0.22) and weak negative correlation with screen time (r=-0.21).

Systolic blood pressure correlated positively with thrombomodulin level (r=0.36) and weaker correlation with E-Selectin (r=0.27) and weak positive correlation with ACR level (r=0.24).

Diastolic blood pressure correlated negatively with RHI (r=-0.34) and positively with HbA1c (r=0.38), LDL (r=0.35), p-Selectin (r=0.31), thrombomodulin (r=0.31), adiponectin (r=0.29) and negatively correlated with PAQ (r=-0.35). The study showed positive correlation between BMI and LDL and TG (r=0.38 and 0.31) and positive correlation with HbA1c (r=0.37).

Only one of our candidates has autoimmune hypothyroidism, which was controlled by thyroid replacement. Three of the candidates have coeliac disease, 2 of them were compliant with gluten free diet and only one patient was poorly adherent to it leading to high tTG level (tTG=128). There was a negative correlation between the physical activity score and the diastolic blood pressure (r=-0.35), LDL (r=-0.39), TG (r=-0.30) and with leptin (r=-0.31). Screen time showed positive correlation with HbA1c (r=0.31), total daily dose of insulin (r=0.35), TG (r=0.33) and LDL (r=0.29). Transient microalbuminuria was detected in 4 patients.

Microalbumin to creatinine ratio correlated positively with E-Selectin (r=0.32).

Discussion

In this study, we hypothesized an association between poor metabolic control and endothelial dysfunction in adolescents with Type 1 diabetes. In our study, patients with lower RHI were significantly younger that patients with higher RHI, this is similar in other studies using reactive hyperaemia index to assess endothelial function [50-54]. However, Kelly et al study using FMD score did not show the same age variability when using flow mediated dilation to assess Endothelial function [55], they postulated that the use of same size finger probes could be the reason. Currently only one size finger probes are available for this machine. In Kelly et al study there was a correlation with blood pressure and endothelial dysfunction using FMD, we found similar correlation between blood pressure and Reactive hyperaemia index, which demonstrates the negative impact of the high blood pressure on endothelial function.

We did not find a correlation between Hba1c and RHI and this finding was demonstrated as well in a recent study by Mahmud et al. [56]. However, others have shown a correlation between RHI and Hba1c [45,57]. In our study RHI strongly correlated with the inflammatory marker p-Selectin and had positive correlation with sICAM and thrombomodulin indicating endothelial dysfunction which was demonstrated in other studies as well [7,42].

We found that higher HbA1c was associated with higher levels of inflammation as demonstrated by higher levels of p-Selectin (r=0.55), Thrombomodulin (r=0.31), adiponectin (r=0.33), which is consistent with other studies [7,42,58,59]. Higher HbA1c was found to be significantly correlated to dyslipidaemia through the positive correlation with LDL (r=0.55) which was demonstrated in previous study [60]. Though LDL level did not correlate with RHI, it correlates significantly with HbA1c, BMI and DBP, underlining the important association between a heathy lifestyle and vascular health. These results agrees with other studies defining dyslipidaemia as a risk factor for vascular disease [3,60,61]. On the other hand, HDL had more significant association with lower level of thrombomodulin demonstrating its protective effect on vascular health [62].

There was no gender difference in RHI, consistent with other studies [49,51]. However, our results show that the duration of diabetes has some effect on endothelial function regardless of age, evidenced by the weak negative correlation between age and RHI. Other studies showed correlations between duration of diabetes and impaired endothelial function using FMD and IMT [63-65].

The negative correlation between RHI and diastolic blood pressure and p-Selectin and the positive correlation between blood pressure and inflammatory markers demonstrate the importance of blood pressure control on vascular health in adolescents with T1D. This agrees with other studies showed correlations between the

elevated blood pressure and higher levels of inflammatory markers [26,27,66].

The correlation between the RHI and the physical activity score was weakly positive (r=0.22) and weakly negative with screen time (r=-0.21). The Physical Activity Questionnaire (PAQ-A) is a quick and easy way to evaluate the overall activity level over previous 7-day period during school time. This questionnaire though, giving us a strong sense of the general activity [67]. It did not evaluate the intensity of the physical activity, caloric expenditure or objectively record the duration of activity [43]. Our study did not show a correlation between physical activity and screen time on BMI. However, beneficial effects of physical activity on blood pressure, LDL and TG levels were demonstrated in this study as shown by the negative correlations with same (r=-0.35, -0.39 and -0.30). The effect of sedentary lifestyle and impaired lipid profile was demonstrated by the correlations between the screen time and lipid profile. These findings have been found in other studies [68-70].

The harmful effect of screen time on glycaemic control and total daily dose of insulin were demonstrated in this study (r=0.31 and 0.35). Similar findings were obtained in different studies [71]. It is well known that physical activity increases the glucose uptake by the muscles, reduces blood sugar level and improves insulin sensitivity. To fully evaluate the effect of physical activity on vascular health we recommend further study where physical activity is assessed in a more objective way (as using accelerometers or joining observed weekly exercise classes) and follow up its effect on not only on body weight but also on body composition, together with its effect on RHI, inflammatory markers, glycaemic control, lipid profile and blood pressure. Microalbuminuria correlated with higher inflammatory markers E-Selectin (r=0.32) agreeing with other studies [13,32].

There was no age matched control group without diabetes in this study. However, assessment of endothelial function using the Endo PAT (Itamar Medical) has been validated in previous studies in children and adolescents with and without diabetes [45,55,72].

Impaired endothelial function can start early in life and in this study; it correlated with elevated diastolic blood pressure and elevated p-selectin level. Maintaining a healthy life style and optimal glycaemic control improves the general health and in particular vascular health of those with T1D and should be actively encouraged.

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