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Blood pressure disturbances and endothelial dysfunction markers in children and adolescents with type 1 diabetes

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ABSTRACT

Objective: Being the earliest step on the way to atherosclerosis, endothelial dysfunction is particularly escalated in diabetes. This study aimed at assessing endothelial dysfunction and blood pressure disturbances in young patients with type 1 diabetes mellitus (T1DM) and defining their interrelations. **Methods**: The study group comprised 52 children and adolescents aged 14.07 ± 3.03 years, with T1DM duration 5.13 ± 2.18 years. 20 healthy controls with similar age and sex distribution were included. Chosen serum biochemical markers of endothelial damage: intercellular adhesion molecule-1 (sICAM-1), vascular cell adhesion molecule-1 (sVCAM-1), sE-selectin, tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) as well as ambulatory blood pressure monitoring (ABPM) were performed in all subjects. **Results**: Patients with T1DM displayed significantly higher concentrations of chosen markers of endothelial dysfunction compared to controls (sVCAM-1 (ng/ml): 951.56 ± 330.68 vs. 710.35 ± 162.12, TNF-α (pg/ml): 16.63 ± 8.32 vs. 9.41 ± 4.23, IL-6 (pg/ml): 3.38 ± 1.31 vs. 2.45 ± 0.81; $p < 0.05$). Within the study group subjects with an abnormal ABPM reading had significantly higher concentrations of sE-selectin compared with subjects with normal ABPM (in ng/ml: 45.71 ± 15.63 vs. 32.42 ± 11.95; $p < 0.01$). The study revealed a significant positive correlation between sE-selectin and systolic as well as diastolic pressure loads during the day period (respectively: $r = 0.46$, $r = 0.60$; $p < 0.01$). **Conclusions**: Endothelium dysfunction may be present early in the course of T1DM in children and adolescents. It seems to be related with blood pressure disturbances which highlights the need to intensify treatment in this group of patients.

1. Introduction

Endothelium forms an internal lining of all vessels in human body. Being strategically situated between the blood stream and surrounding tissues it has got numerous functions crucial for maintaining intravascular homeostasis [1]. Endothelial cells play an important role in vascular tone regulation, hemostasis and fibrinolysis [2–4]. With the negative charge of its intact surface and produced substances this tissue actively resists thrombosis [3,4]. Another essential feature of endothelium is the interaction with circulating white blood cells facilitating their transmigration through the vessel wall [2,5,6]. In diabetes hyperglycemia and related pathological biochemical processes trigger damage to the endothelial cells causing their dysfunction. The dysfunctional endothelium adopts prothrombotic, proinflammatory and vasoconstrictive phenotype promoting the development of atherosclerosis [2,3,7]. Many different measures of endothelium status assessment are available. One of them is a constantly increasing group of biochemical markers like intercellular adhesion molecule-1 (sICAM-1), vascular cell adhesion molecule-1 (sVCAM-1), von Willebrandt factor (vWF), plasminogen activator inhibitor-1 (PAi-1), tissue plasminogen activator (TPA), thrombomodulin (sTM), tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-1 (IL-1), high-sensitive C-reactive protein (hsCRP), endothelin-1 (ET-1). A growing number of studies showed elevated levels of those substances even in children with diabetes [8–11].

Hypertension (HT) is a classical risk factor of the peripheral vessels disease. Its prevalence is known to be 1.5–3 times higher in patients with diabetes than in general population [12,13]. It was previously thought to occur mostly in adults but similar data come from developmental population as well [14–16]. HT produces shear

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stress to the endothelial cells damaging them physically and causing endothelial dysfunction [1,2,17].

The accumulation of different endothelium-hostile pathological factors in diabetes makes it possible for the endothelial dysfunction to appear even in children. Most of the existing data come from an adult population of patients with type 2 diabetes. Knowledge about endothelium dysfunction in children with type 1 diabetes (T1DM) is still limited. The available studies usually focus on single markers of endothelial dysfunction and vary in results. Moreover data on the influence of high blood pressure on the endothelium status in children with type 1 diabetes are scarce. Only few studies focus on this problem, mostly not analyzing the blood pressure profiles of the studied groups in a complex way [8,20].

The aim of this study was to assess endothelial function in children and adolescents with type 1 diabetes in relation to blood pressure. We hypothesized that the endothelium dysfunction could be connected with blood pressure disturbances.

2. Subjects, materials and methods

Study group consisted of 52 children and adolescents with type 1 diabetes (33 girls) with the mean age 14.07 ± 3.03 years, mean diabetes duration 5.13 ± 2.18 years and mean $HbA1_c$ − 7.18 ± 1.04% (55 ± 10.8 mmol/mol). The subjects were hospitalized in the Department of Pediatrics, Endocrinology and Diabetes of the Medical University of Silesia in Katowice (Poland) during 2007–2010. The medical records of those individuals from the Diabetes Outpatient Clinic of the Upper Silesia Child Health Center in Katowice were also used in the analysis. The inclusion criteria were: age between 8 and 18 years, duration of diabetes at least 3 years for prepubertal children and at least 2 years for pubertal individuals, no known chronic disease (especially Hashimoto or celiac disease), no acute inflammation for 3 weeks before and at the day of the examination, no drugs taken except insulin, no smoking, informed consent of the guardians and participants.

A control group comprised 20 healthy peers (12 girls) with similar age and sex distribution as in the study group. Volunteers were invited to participate in the study after completing the same inclusion criteria as in the study group (apart from diabetes). The subjects were recruited from friends of patients with diabetes. The number of controls was limited because of the substantial difficulties with the recruitment and limitations set by Bioethical Committee.

Medical history including data about previous and current course of diabetes treatment (i.e. mean $HbA1_c$ from the diabetes onset done once every three months, daily insulin dose in units/kg body weight/24 h), physical examination and laboratory tests were performed in the study group. Fasting concentrations of chosen adhesion molecules (sICAM-1, sVCAM-1, sE-selectin) and proinflammatory cytokines (TNF-α, IL-6) were tested using commercial kits (R&D Systems). Microalbuminuria was determined by means of 10-h night collection samples and immunologic chemiluminescence method. Thyroid function tests (TSH, fT4), thyroid antibodies: thyroid peroxidase antibodies (ATA) and thyroglobulin antibodies (ATG) as well as tissue transglutaminase antibodies (IgAtTG) in order to fulfill inclusion criteria were also evaluated. Moreover a 24-h blood pressure monitoring (ABPM) using Spacelabs 90217 device with age-fitted cuffs was performed. It was set to measure blood pressure (BP) every 20 min during the day period (6:00 a.m.–10:00 p.m.) and every 30 min during the night period (10:00 p.m.–6:00 a.m.). The cut-off values of blood pressure were set on the basis of the centile charts for age, sex and height and according to the guidelines of "The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents" [21]. Patients whose systolic and/or diastolic blood pressure load during any period was beyond 40% were considered BP-abnormal. Those with blood pressure fall during the night lower than 10% were classified as non-dippers. $HbA1_c$ in our Department as well as in aforementioned Diabetes Outpatient Clinic is measured using the HPLC method according to DCCT standards.

Table 1
Clinical characteristics of the study and control group.

	Study group $N = 52$	Control group $N = 20$	Statistical significance of differences
Age (years)	14.07 ± 3.03 [13.23 ÷ 14.92]	13.09 ± 3.05 [11.66 ÷ 14.51]	p = NS
Height (cm)	164.49 ± 16.37 [159.93 ÷ 169.05]	157.38 ± 15.10 [150.31 ÷ 164.44]	p = NS
Body weight (kg)	58.15 ± 15.26 [53.90 ÷ 62.40]	50.64 ± 19.44 [41.54 ÷ 59.73]	$p < 0.01$
BMI (kg/m^2)	21.02 ± 2.67 [20.28 ÷ 21.77]	19.81 ± 4.09 [17.89 ÷ 21.72]	$p < 0.05$
Age at onset of diabetes (years)	9.02 ± 0.60 [8.82 ÷ 9.22]		
Diabetes duration (years)	5.09 ± 1.97 [4.39 ÷ 5.79]		
Mean $HbA1_c$ (%/mmol/mol)	7.17 ± 0.99/ 55 ± 10.8 [6.82 ÷ 7.52]		
Daily insulin requirement (units/kg body weight/24 h)	0.84 ± 0.18 [0.78 ÷ 0.90]		

Data are presented as mean ± standard deviation (SD) and [95% CI].

After physical examination the same laboratory tests including: TSH, fT4, ATA, ATG, IgAtTG, sICAM-1, sVCAM-1, sE-selectin, TNF-α, IL-6 and ABPM were performed in the control group (except microalbuminuria).

The following descriptive statistics and their 95% confidence intervals (noted as 95%CI) were estimated per every continuous variable under investigation: mean, standard deviation, median, lower and upper quartile, minimum and maximum value. Lilliefors test was applied to verify the hypothesis on distribution normality, while homogeneity of variances was checked with F test. Hypotheses on equality of variances and/or median values were verified by t test (for Gaussian distributions) or Mann–Whitney U test (in case of non-Gaussian distributions). The association between variables was measured by Pearson's or Spearman's correlation coefficients (for Gaussian and non-Gaussian distributions respectively) and the tests on their significance. The logistic regression algorithm was applied to find the discriminant function distinguishing between patients and healthy controls. Due to the small sample sizes, the forward selection algorithm was applied to the prefiltered set of features accompanied by Akaike information criterion (AIC) and likelihood ratio test for model selection. The initial set of prefiltered features was constructed of those with p-value less than 0.2 in SISO comparative analysis. The linear regression technique was used to construct an adjusted model of interactions between a vascular cell adhesion molecule-1 marker and some clinical parameters. In case of the skewed distributions of the analyzed variables, the Box–Cox power transformation was applied to correct for the departures from normality. The age dependent standardization was used to the anthropometric measurements (patient height and weight) in the form $SDS = (X - X_{sr})/SD$ per every age group independently. The F statistics was used to assess the quality of model fitting.

The results were assumed as statistically significant if p-values were less than 0.05.

The study gained a positive opinion of the Bioethical Committee of the Medical University of Silesia in Katowice no. NN-6501-82/07.