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Soluble adhesion molecules (sICAM-1, sVCAM-1) and selectins (sE selectin, sP selectin, sL selectin) levels in children and adolescents with obesity, hypertension, and diabetes

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Abstract

The attachment of monocytes and lymphocytes to endothelial cells, which initiates atherosclerosis, arises under the influence of adhesion molecules. The preclinical phase of this disease lasts many decades, and this provides an opportunity for the presymptomatic detection of high-risk subjects. We evaluated levels of the adhesion molecules: sICAM-1 (soluble intercellular adhesion molecule 1), sVCAM-1 (soluble vascular adhesion molecule 1), sE selectin, sP selectin, and sL selectin in children with atherosclerosis risk factors (n = 123, mean age 15.1 years) (obese [n = 17], hypertensive [n = 25], obese with hypertension [n = 30], type 1 diabetic [n = 51]). Twenty-seven healthy children formed the control group, mean age 15.2 years. sICAM-1 was higher in the study group compared with control (314.1 ± 61 vs 264.9 ± 55 ng/mL, $P < .01$). The same was found for sVCAM-1 (513.7 ± 187 vs 407.9 ± 76 ng/mL, $P < .05$) and E selectin (86.04 ± 33.6 vs 62.1 ± 20.3 ng/mL, $P < .01$). sP-selectin and sL-selectin levels were not different compared with controls. E selectin correlated with body mass index (BMI; $r = 0.18$, $P = .03$), total cholesterol ($r = 0.2$, $P = .016$), and triglycerides ($r = 0.22$, $P = .008$). sICAM-1 correlated with BMI ($r = 0.19$, $P = .019$) and systolic blood pressure ($r = 0.13$, $P = .045$). In multiple linear regression analysis, sE selectin was found to be associated with triglycerides ($R^2 = 0.29$, $P = .045$), sICAM-1 dependent on BMI ($R^2 = 0.58$, $P = .047$), and sVCAM-1 dependent on total cholesterol ($R^2 = 0.51$, $P = .006$). Elevated concentrations of sICAM-1, sVCAM-1, and E selectin were found in obese, hypertensive, and diabetic children. We conclude that endothelial activation appears in these children, and adhesion molecules are related to the earliest stages of atherosclerosis.

1. Introduction

Vascular endothelium is currently being regarded as not a passive barrier between flowing blood and the vascular wall, but as a highly specialized metabolically active tissue [1,2]. The most important changes that occur during the activation of endothelial cells, under the stimulatory influence of various factors, consist of an increased expression of adhesion molecules and selectins, whose soluble forms can be detected in blood. This increased expression leads to the rolling, activation, and firm adhesion of leukocytes to the endothelium [3,4]. Although adhesion molecules are vital for the normal development and function of the heart and blood vessels, they have also been implicated in the pathogenesis of cardiovascular disease [5-7].

Damage of the endothelium in the form of its desquamation is not an essential component of and is typically absent in the first stage of the atherosclerotic process. Attachment of monocytes and lymphocytes to endothelial cells, which initiates the process of atherosclerosis, arises under the influence of cellular adhesion molecules (CAMs) [7]. Binding of these cells to the endothelium requires the interaction of integrin on the surface of leukocytes with intercellular adhesion molecule 1 (ICAM-1), VCAM-1 (vascular adhesion molecule 1), and selectins on the endothelium [6]. By losing its protective properties and allowing the unopposed action of atherogenic factors on the vessel wall, dysfunctional endothelium is a major promoter of atherosclerosis [1]. After transmigration into the vessel wall, leukocytes release various bioactive molecules, which initiate the development of lipid deposits and foam cells as well as proliferation of smooth muscle cells [7,8].

Although the main clinical consequences of atherosclerosis such as myocardial infarction or stroke usually occur

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in adults, the atherogenic process actually begins during childhood, the time of onset of fatty infiltration of the vasculature [9]. This preclinical phase lasts many decades, and this pattern of the disease provides an opportunity for the presymptomatic detection, identification of high-risk subjects, and the application of appropriate prevention strategies [10,11].

Risk factors for atherosclerosis appear during childhood and are already by this time associated with atherosclerotic changes in vessel walls. The process of atherosclerosis is accelerated in children in whom multiple risk factors for the disease are present [12]. There is a great need to find and evaluate noninvasive methods to ensure a reliable detection of high-risk young subjects during the long presymptomatic phase of the disease, during which such endothelial changes are entirely reversible [2,10,13].

The aim of the study was to evaluate the concentrations of soluble forms of adhesion molecules ICAM-1 and VCAM-1 and selectins E selectin, P selectin, and L selectin in children and adolescents with a presence of atherosclerosis risk factors (obesity, hypertension, and diabetes), and to compare these with healthy controls, as well as to find out the correlations between these molecules and studied parameters such as lipid levels, blood pressure values, and body mass index (BMI). We also wanted to discover if evaluation of concentration of any of these molecules can be helpful in detection of endothelial activation in identification of high-risk young patients.

2. Methods

2.1. Subjects

The study consisted of patients of the 2nd Department of Children's Diseases of the Medical University of Bialystok Poland and its related outpatient clinics for diabetes, cardiology, and endocrinology. In total, 123 (69 boys and 54 girls) children and adolescents were included, with the mean age being 15.1 ± 3.3 years (age 8-20 years). The group was divided according to their diagnosis. Group A (n = 17) consists of obese children; B (n = 30) consists of children diagnosed with obesity and coexisting hypertension; C (n = 25) consists of children with hypertension, and D (n = 51) consists of children with diabetes. Twenty-seven (15 boys and 12 girls) healthy nonobese children formed the control group, with the mean age of 15.2 ± 2.1 years (range 11-19 years), with no family history of cardiovascular disease. The characteristics of the groups are presented in Table 1.

Obesity was defined when the BMI (in kilograms per squared meter) exceeded the 95th percentile, matched according to age and sex, using percentile charts for the assessment of somatic development in children and adolescents [14]. Children with secondary obesity were not included in the study. High arterial blood pressure was diagnosed using a 24-hour ambulatory blood pressure monitoring system (ABPM), using the Medilog DX apparatus (Oxford, Abingdon, UK). Hypertension was diagnosed when high measurements recurred frequently, that is, at least 30% of the 24-hour recordings exceeded the 95th percentile, matched for age and sex [15]. Mean systolic (SBP) and diastolic (DBP) blood pressure values were calculated from ABPM. For all children, an underlying cause for their hypertension, such as hormonal, renal, or cardiac, was sought. Such children were excluded from the study. Diabetes was diagnosed using the criteria defined by the American Diabetes Association, 1997 [16]. Children studied had solely diabetes mellitus type 1.

2.2. Measurements

For analysis, 10 mL of blood was taken from the left cubital vein, which was a morning sample taken before breakfast, after an overnight (8-12 hours) fast. To assess adhesion molecules and selectins levels, serum samples were collected, frozen, and stored at a temperature of −70°C until analysis was performed. The concentration of

Table 1
General characteristics of the study groups and analysis of the lipid levels

	Study group	Group A	Group B	Group C	Group D	Control group
Number	123	17	30	25	51	27
Boys/girls	69/54	8/9	18/12	15/10	28/23	15/12
Age (y)	15.1 ± 3.1	13.1 ± 3.1	14.8 ± 2	14.9 ± 1.9	15.5 ± 3.8	15.2 ± 2.1
Height (m)	1.67 ± 0.1	1.56 ± 0.1	1.7 ± 0.1	1.7 ± 0.15	1.64 ± 0.1	1.66 ± 0.1
Body mass (kg)	69.8 ± 19	68.1 ± 13	89.8 ± 20.2	65.3 ± 13.3	60.8 ± 13.5	55.1 ± 9.7
BMI (kg/m^2)	24.7 ± 4.9	27.6 ± 2.9	29.6 ± 4.7	22 ± 2.2	22.2 ± 3.7	19.6 ± 2.4
Mean SBP (mm Hg)	127 ± 16.6	119.8 ± 11	142.3 ± 15.2	134.7 ± 13.1	116.4 ± 10.8	115.9 ± 8.2
Mean DBP (mm Hg)	75 ± 9.3	71 ± 7	81.3 ± 9.5	82.9 ± 7.3	70.7 ± 7.9	70.8 ± 8.3
Total cholesterol (mmol/L)	4.54 ± 0.8*	4.11 ± 0.5	4.75 ± 0.8**	4.20 ± 0.8	4.7 ± 0.8**	4.15 ± 0.6
LDL cholesterol (mmol/L)	2.62 ± 0.6	2.32 ± 0.4	2.81 ± 0.8	2.28 ± 0.7	2.78 ± 0.6	2.4 ± 0.5
HDL cholesterol (mmol/L)	1.29 ± 0.3	1.18 ± 0.2	1.16 ± 0.2	1.3 ± 0.3	1.37 ± 0.2	1.24 ± 0.1
Triglycerides (mmol/L)	1.33 ± 0.7*	1.32 ± 0.4**	1.63 ± 1**	1.22 ± 0.5*	1.21 ± 0.5*	0.94 ± 0.3

Data are presented as mean ± SD. Groups A, obese; B, obese and hypertensive; C, hypertensive; and D, diabetic children. HDL indicates high-density lipoprotein.

* $P < .05$ compared with control group.

** $P < .01$ compared with control group.

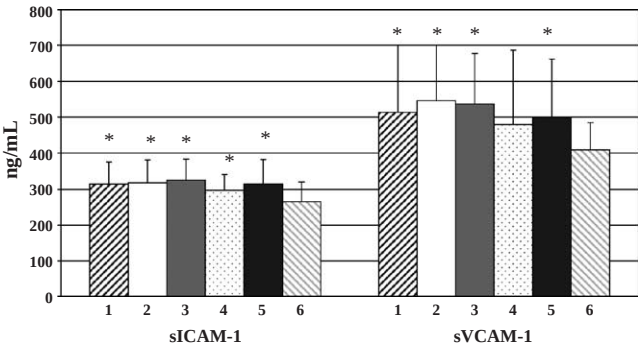

Fig. 1. sICAM-1 and sVCAM-1 levels in the study groups. Data are presented as mean ± SD. *$P < .05$ compared with control group. 1, Whole study group; 2, obesity; 3, obesity and hypertension; 4, hypertension; 5, diabetes; 6, control group.

adhesion molecules and selectins was determined immunoenzymatically (Parameter Human Immunoassays, R&D Systems, Inc, Minneapolis, Minn) with the use of ELx 800 Automated Microplate Reader, Bio-Tek Instruments, Winooski, Vt, USA. The intra-assay and the interassay precision coefficients of variation (%) were as follows: soluble ICAM-1 (sICAM-1) 3.3/6.0, soluble VCAM-1 (sVCAM-1) 4.3/8.5, sE selectin 4.8/5.7, sP selectin 4.9/8.8, and sL selectin 2.5/8.8. Concentrations of lipid parameters were determined by enzymatic methods using commercial kits. Analysis was performed in the hospital's laboratory using standard laboratory instruments (Hitachi 912, La Roche, Tokyo, Japan). Low-density lipoprotein (LDL) concentration was by the Friedewald equation.

We obtained the agreement of the Local Bioethical Committee, based at the Medical University of Bialystok, Poland. Parents and children were informed as to the nature and purpose of the study. Parents gave their written consent. Children vocally issued their consent.

2.3. Data analysis

Statistical analysis was performed with the use of the computer program, Statistica 5.0. For normally distributed variables, the unpaired Student t test was used, and for not normally distributed variables, the Mann-Whitney U test was used. The data are presented as mean and SDs. For the purpose of determining the significance of differences between the groups of ill children (A, B, C, D), 1-way analysis of variance and post hoc Tukey test to control for multiple comparisons were performed. Correlations between adhesion molecules, selectins and lipid parameters, BMI, and blood pressure values were analyzed by Spearman method. Multiple linear regression analysis was performed to verify measured parameters as being statistically significant. In our regression model, we verified E selectin, P selectin, and L selectin, as well as sICAM and sVCAM as dependent variables, and we included BMI, total cholesterol, triglycerides, and blood pressure values as independent variables. A P value $<.05$ was considered to be statistically significant.

3. Results

Table 1 summarizes the results of routine lipid analysis. Total cholesterol was higher in the study group compared with controls (4.54 ± 0.8 vs 4.15 ± 0.6 mmol/L, $P < .05$). The highest levels were found in groups of obese and hypertensive children (group B), 4.75 ± 0.8 mmol/L ($P < .01$), and diabetic children (group D), 4.7 ± 0.8 mmol/L ($P < .01$). Triglyceride levels were significantly higher in all the selected groups of patients. The mean level was 1.33 ± 0.7 mmol/L in the whole study group vs 0.94 ± 0.3 mmol/L in controls ($P < .05$), and the highest level was found in the group of obese and hypertensive patients (1.63 ± 1 mmol/L) ($P < .01$).

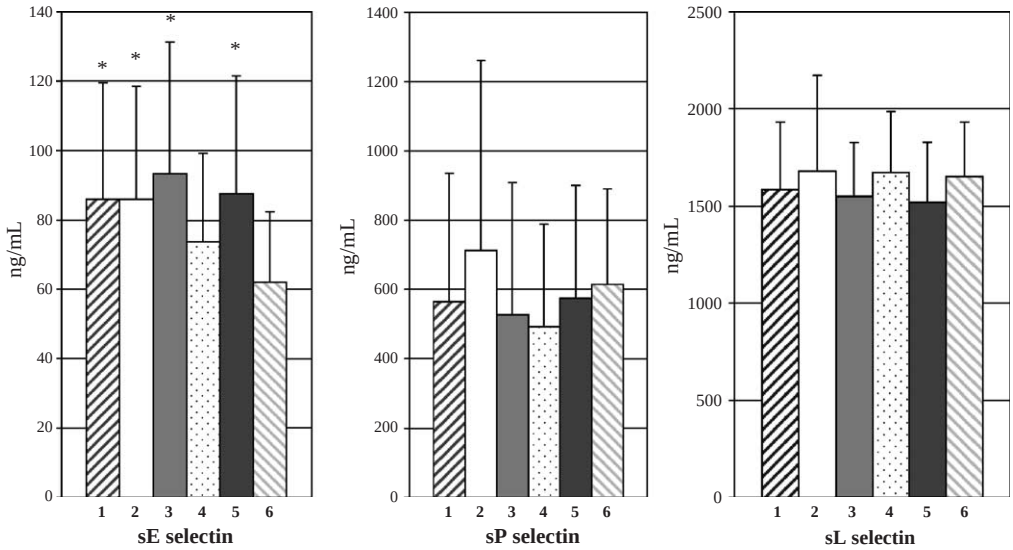

Fig. 2. sE-selectin, sP-selectin, and sL-selectin levels in the study groups. Data are presented as mean ± SD. *$P < .05$ compared with control group. 1, Whole study group; 2, obesity; 3, obesity and hypertension; 4, hypertension; 5, diabetes; 6, control group.

The sICAM-1 concentration was higher in the whole study group compared with control (314.1 ± 61 vs 264.9 ± 55 ng/mL, $P < .01$). Significant differences were found for all selected groups—in the obese children group, sICAM-1 level was 317.9 ± 63 ng/mL ($P < .01$); in the obese and hypertensive group, 325.5 ± 58ng/mL ($P < .01$); in the hypertensive children, 296.8 ± 44 ng/mL ($P < .05$); and in the diabetic children, 314.5 ± 68 ng/mL ($P < .01$) (Fig. 1). Variance analysis did not reveal any significant differences in sICAM-1 concentrations between groups of children with atherosclerosis risk factors when the control group was excluded. sVCAM-1 level was significantly higher in the whole study group—513.7 ± 187 vs 407.9 ± 76 ng/mL in the control group ($P < .05$). Concentrations of sVCAM-1 were also found to be higher in the obese children, 546.5 ± 153 ng/mL ($P < .01$); in the obese and hypertensive group, 536.02 ± 141 ng/mL ($P < .05$); and in the diabetic group, 499.4 ± 162 ng/mL ($P < .05$) (Fig. 1). Analysis of variance did not show significant differences between the study groups of ill children.

Fig. 2 presents results of the selectin concentrations. Significant differences were found for E-selectin levels. In the whole study group, it was 86.04 ± 33.6 ng/mL, compared with that of the control group—62.1 ± 20.3 ng/mL ($P < .01$). Such similar significantly higher concentrations of E selectin were observed for the obese children group (86 ± 32.6 ng/mL, $P < .01$), the obesity and hypertension group (93.4 ± 37.9 ng/mL, $P < .01$), the hypertension group (73.8 ± 25.5 ng/mL, not significant [ns]), and the diabetic group (87.6 ± 34 ng/mL, $P < .01$). The highest levels were found in the group of children with obesity and accompanying hypertension, although analysis of variance did not reveal significant differences in E-selectin levels between groups of ill children. The mean sP-selectin concentration in the experimental group was 564.6 ± 371 ng/mL and did not differ significantly from the sP-selectin level of the control group: 615.6 ± 275 ng/mL (ns). In all selected groups of patients, sP-selectin levels did not differ significantly compared with the control group. The sL-selectin concentration in the experimental group was 1584.8 ± 348 ng/mL and did not significantly differ from that of the control group—1652.1 ± 281 ng/mL (ns). We did not find any significant differences in sL-selectin levels in all selected subgroups of patients (Fig. 2).

Correlation analysis between adhesion molecules and BMI, lipid levels, and blood pressure values, including whole study group, showed significant correlations between the following : E selectin with BMI ($r = 0.18$, $P = .03$), E selectin with total cholesterol ($r = 0.2$, $P = .016$), and E selectin with triglycerides ($r = 0.22$, $P = .008$). sICAM-1 correlated significantly with BMI ($r = 0.19$, $P = .019$) and with SBP ($r = 0.13$, $P = .045$). Statistically significant, interesting correlations were also found in selected groups of patients: in obese children, sVCAM-1 levels correlated with LDL cholesterol ($r = 0.43$, $P = .02$). In obese and hypertensive children, sE selectin correlated with total cholesterol ($r = 0.38$, $P = .038$) and LDL ($r = 0.38$, $P = .042$), sICAM-1 levels correlated with total cholesterol ($r = 0.44$, $P = .015$) and triglycerides ($r = 0.44$, $P = .023$), and sP selectin correlated with SBP ($r = 0.38$, $P = .038$). In hypertensive children, we found significant correlations for sP selectin—with SBP ($r = 0.5$, $P = .011$) and LDL ($r = 0.42$, $P = .04$). In diabetic children, sE selectin correlated significantly with DBP values ($r = 0.3$, $P = .042$) and with triglycerides ($r = 0.3$, $P = .03$), and sICAM-1 correlated with DBP ($r = 0.25$, $P = .043$). Multiple linear regression analysis was performed, including whole study group, to verify the statistical significance of these associations. In the regression models, sE selectin was found to be dependent on triglycerides ($R^2 = 0.29$, $B = 0.09$, $P = .045$), sICAM-1 dependent on BMI ($R^2 = 0.58$, $B = 3.4$, $P = .047$), and sVCAM-1 dependent on total cholesterol ($R^2 = 0.51$, $B = 3.3$, $P = .006$).

4. Discussion

Our study showed increased concentrations of the adhesion molecules sICAM-1, sVCAM-1, and E selectin in children and adolescents burdened with risk factors for atherosclerosis such as obesity, hypertension, and diabetes. The highest concentrations of these molecules appeared in obese children with coexisting hypertension, whereas lean hypertensive children showed only higher concentrations of the molecule sICAM-1. Current literature does not show much research concerning adhesion molecules or endothelial activation in children. Nash et al [17] showed the concentration of ICAM-1 and VCAM-1 to be significantly greater in children than in adults, and these concentrations were found to decline with age. A negative correlation between the age of young patients and the concentrations in adhesion molecules supports the findings of Ohta et al [18], who first described the clinical usefulness of assessing adhesion molecules as a marker of the first phase of atherosclerosis in children. Elhadd et al [19] showed, as in our study, an increased sICAM-1 and sE selectin in children with diabetes type 1, with an absence of the clinical features of angiopathy.

Studying the concentration of certain adhesion molecules in correlation to lipid levels in children showed in lean healthy children a significant dependence between sICAM-1, sVCAM-1, and triglyceride concentrations. It has been demonstrated that there is a significant positive correlation between the concentrations of apolipoprotein B with sICAM-1, and a negative correlation between this adhesion molecule with LpA-I [18]. Our results showed a similar significant correlation between the parameters of lipid metabolism and adhesion molecules. E selectin correlated with the cholesterol and triglyceride concentration. Regression analysis showed significant correlations between E selectin and triglycerides, and sVCAM-1 with cholesterol. Therefore, it would seem that abnormal lipid metabolism may lead to activation of the endothelium in young people. In adult patients with hypertriglyceridemia and low concentrations of high-density lipoprotein cholesterol, a significantly

higher concentration of sICAM-1, sVCAM-1, and E selectin has been demonstrated. Omega-3 polyunsaturated fatty acids applied in the diet in these patients caused reduction in triglyceride concentrations as well as the significant decrease in sICAM-1 and E selectin [20].

Ferri et al [21] showed an increased concentration of sVCAM-1, sICAM-1, and E selectin in adults who were obese, compared with adults who were healthy or only had hypertension. An interesting and important observation of this study is the significant fall in concentration of adhesion molecules 12 weeks after a low-calorie diet, with a resultant weight loss. This link between obesity, cardiovascular diseases, and endothelial dysfunction might result from an association between obesity and insulin resistance, which has been confirmed by recent studies [22,23]. Our study demonstrated a significant association between the BMI and sICAM-1 and sE selectin.

The analysis of lean hypertensive patients showed a significant rise in the concentration of adhesion molecules in patients with coexisting glucose intolerance and hyperlipidemia [24]. The use of angiotensin-converting enzyme inhibitors resulted in a significant fall in the concentration of adhesion molecules independently of hypotensive effect of the treatment. The group of adult males showed a significant association between sICAM-1 and hypertension, which was found to be independent of other risk factors [25]. Our study showed a significant association between sICAM-1 and SBP. A positive correlation was also found between sICAM-1, sE selectin, and DBP values.

Some of the correlations we found in our study are small, although significant. From statistical point of view, the only small component of variability may be accounted for by the adhesion molecules. We state, however, that these correlations are worth discussing to emphasize the possibility to reverse endothelial activation by reducing lipid concentration, body mass, or blood pressure.

The results of the findings of studies in adults with advanced atherosclerosis showed significant increases in sICAM-1 and sVCAM-1 in patients with coronary heart disease, where there was myocardial infarction, or sudden cardiac death [26]. In the long-term study of Ridker et al [27], they found a significant rise in the adhesion molecule sICAM-1 in apparently healthy males who had a heart attack during a 9-year period of follow-up. This unique observation would appear to confirm the hypothesis that endothelial cell dysfunction and chronic inflammation of the vessel wall develop early, many years preceding the onset symptoms of coronary heart disease.

The most frequently studied selectin, E selectin, appears to be important in detection of the destruction of the endothelium in coronary heart disease [28-30]. Elevated concentrations of E selectin are characteristic for patients with moderate coronary heart disease, whereas for patients with more advanced disease, a rise in ICAM-1 predominates [30]. E selectin, along with other adhesion molecules such as ICAM-1 and VCAM-1, showed a significant correlation with risk of death of cardiovascular origin in patients already diagnosed to have coronary heart disease. With regard to the evaluation of P selectin and L selectin in our patients, we did not see a significant difference between their mean concentrations, nor was any significant correlation found. P selectin is regarded as being above all a marker of platelet activation [31], although some authors also regard it to be a marker of endothelial activation [32]. Lip et al [33] demonstrated increased concentrations of P selectin in patients with essential hypertension, which they explained as being due to platelet dysfunction in such patients. Barbaux et al [34] described significantly greater concentrations of P selectin in patients with coronary heart disease developed before the age of 55 years. The role and significance of L selectin in the process of atherosclerosis are uncertain. Albertini et al [35] observed significantly lower concentrations of L selectin in patients with diabetes type 2 who had symptoms of coronary artery disease. These authors postulated that the reduced concentrations of L selectin were due to their diminished release from circulating leukocytes into serum, and an increased binding activity of leukocytes to damaged endothelium in the process of atheroma formation.

The importance of obesity, hypertension, or diabetes in predicting cardiovascular risk in adults is well known. There is, however, little known about the predictive value of these disorders in young population. In the long-term prospective study of the cardiovascular risk factors in the population of the Bogalusa Heart Study, it was shown that 50% of the children aged 2 to 15 years, studied at necropsy, had atherosclerotic changes in coronary arteries. The extension of the fatty streaks in the coronary arteries was 8.5 times greater and the presence of fibrous plaques 12 times greater in children and young adults with multiple atherosclerosis risk factors such as obesity, hypertension, hyperlipidemia, or diabetes [9,12]. The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study, organized to document the natural history of atherosclerosis and to determine the relation of cardiovascular risk factors to atherosclerosis in young subjects, confirmed the origin of atherosclerosis in childhood, showed that progression toward clinically significant lesions may occur in young adulthood, and demonstrated that progression of atherosclerosis is strongly influenced by coronary heart disease factors [36].

Until very recently, there have been no prospective studies evaluating baseline cellular adhesion molecules concentration and the risk of subsequent vascular disease. However, several data have now been presented, which provide the first evidence that plasma concentrations of adhesion molecules are indeed associated with increased risk of developing clinical coronary disease. Significant association was found between increased concentration of sICAM-1 and risk of future myocardial infarction. The risk among participants of the study with baseline sICAM-1 in the highest quartile was 80% higher compared with those with lower levels (relative risk 1.8) [27]. In another prospective epidemiological evaluation, the risk of future

cardiovascular events increased with increasing quartiles of sP selectin, and women in the highest quartile had 2.2 times higher risk than those in the lowest quartile [32]. In the Atherosclerosis Risk in Communities Study, plasma concentrations of 2 adhesion molecules, sICAM-1 and E selectin, at baseline were both associated with increased future prevalence of coronary heart disease or carotid atherosclerosis [37]. This risk estimates in all mentioned studies appeared to be independent of several lipid and nonlipid cardiovascular risk factors. We allow to advance a hypothesis that assessing adhesion molecules levels may be more accurate and may add more detailed information in predicting the risk of future cardiovascular events in young patients with established risk factors than the traditional predictors alone.

The correlation between cardiovascular disease in parents and the presence of atherosclerosis risk factors in their children is well documented, and the positive family history is regarded as an important independent atherosclerosis risk factor. In our previous studies, we showed that nearly 30% children with obesity, hypertension, or diabetes originate from families where cardiovascular disease is present [38]. Results of some studies have proved that children with positive family history have impaired endothelial function measured as decreased flow-mediated dilatation in brachial arteries [39]. Overexpression of some adhesion molecules shed from the dysfunctional endothelium can be found in these children. The study by Wojakowski and Gminski [40] concerning children from high-risk families and our previous studies [41] concerning diabetic children showed elevated sICAM-1 levels in genetically predisposed children. We suppose that positive family history of cardiovascular disease may cause increase in adhesion molecules levels in children.

Female sex hormones are known to exert a protective role on the vascular endothelial function, but the exact mechanisms of such protection are not known. Studies of the possible regulatory role of female sex hormones changes during the normal menstrual cycle on soluble adhesion molecules are rare and contradictory. Elhadd et al [42] showed that the levels of sICAM-1 did not vary through the cycle, but the mean percentage change in E selectin was significant between early follicular and luteal phases. In the other study by Bonello and Norman [43], sICAM-1 levels were maximal in the early and midfollicular stages and progressively decreased throughout the remainder of the cycle; sVCAM-1 levels also declined in the luteal phase, whereas sE-selectin concentration did not vary markedly across the menstrual cycle. Female sex hormones may have small, although significant, modulating role on adhesion molecules levels [43]. The normal cyclic variation in peripheral adhesion molecules levels may be of particular importance if soluble adhesion molecules have been proposed as biologic markers of certain diseases such as atherosclerosis in women of reproductive age. There is a suggestion that cycle stage should perhaps be accounted for when analyzing results of soluble adhesion molecules assays in cycling women. In our study, we did not consider the menstrual cycle stage in our study girls. The mean age of our study group, 15.1 ± 3.1 years, is the time when menstrual cycle is often not regular yet, and cycles can be physiologically without ovulation, so the hormonal influence on adhesion molecules levels is not possible to assess properly.

It would seem that assessing the concentrations of adhesion molecules in young age groups may be of significant importance, bearing in mind that these molecules are postulated to participate in the earliest phases in the atherogenic process. Continual improvement in understanding the mechanisms, which control this process, strengthens the possibility of therapeutic intervention, especially as the early first phases of atheroma formation are entirely reversible.

5. Conclusions

Elevated levels of sICAM-1, sVCAM-1, and E selectin were found in obese, hypertensive, and diabetic children and adolescents. We conclude that endothelium activation appears in these children and that adhesion molecules are related to the earliest stages of atherosclerosis. Based on our findings and the reports of other studies, it is difficult to definitively determine the role of the various adhesins during the pathogenesis of atherosclerosis and the usefulness of assessing their serum concentration as markers of the early phase of disease. Results of the studies remain ambiguous, sometimes conflicting, and concern various adhesion molecules and various groups of patients. It seems, however, that the greatest evidence regarding endothelial activation can be attributed to the molecules sICAM-1 and E selectin.

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