Association between polycystic ovary syndrome and the risk of subclinical vascular disease in normal-weight women with type 1 diabetes

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KEY WORDS
brachial artery
flow-mediated
dilation, endothelial
dysfunction,
intima–media
thickness, polycystic
ovary syndrome, type
1 diabetes

INTRODUCTION The prevalence of polycystic ovary syndrome (PCOS) among women with type 1 diabetes (T1DM) is higher than in the general population. Both diseases are associated with higher risk of premature atherosclerosis.

OBJECTIVES The aim of our study was to evaluate whether the cardiovascular risks conferred by T1DM and PCOS are additive.

PATIENTS AND METHODS The study group included 78 women divided into 4 groups: 19 women with PCOS and T1DM (T1DM+PCOS), 16 women with T1DM only (T1DM/no-PCOS), 27 women with PCOS only (PCOS), and 16 healthy women (control group). We evaluated the serum concentrations of cardiovascular disease biomarkers: soluble intercellular adhesion molecule 1 (sICAM-1) and soluble endothelial-leukocyte adhesion molecule 1 (sE-selectin). We also assessed brachial artery flow-mediated dilation (FMD) and estimated the intima–media thickness of the common carotid artery (CIMT) by ultrasonography.

RESULTS The serum concentrations of sICAM-1 and sE-selectin were higher in the T1DM+PCOS group compared with women with PCOS only (P = 0.041 and P = 0.002, respectively) and were comparable to those in the T1DM/no-PCOS group. FMD and CIMT did not differ between the groups. In women with T1DM, sICAM-1 positively correlated with body mass index (r = 0.34, P = 0.047), CIMT with daily insulin dose (r = 0.37, P = 0.039), and FMD negatively correlated with diabetes duration (r = –0.42, P = 0.02). In a multivariable logistic regression model, the presence of T1DM, with adjustment for sICAM-1, was the only predictor of sE-selectin concentrations in the whole study group (odds ratio, 8.03; 95% confidence interval, 2.56–13.49; P = 0.005).

CONCLUSIONS The presence of PCOS does not increase the risk of subclinical vascular disease in young lean women with T1DM.

INTRODUCTION Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine disorder in women of reproductive age. According to the Rotterdam criteria, the average prevalence of PCOS is 16.6%.¹ Oligoovulation or anovulation, biochemical or clinical hyperandrogenism, and polycystic ovaries on ultrasonography are the distinguishing characteristics of this endocrinopathy.

The major pathogenic factor of PCOS is probably insulin resistance with compensatory hyperinsulinemia leading to metabolic complications and reproductive dysfunction.²,³ This entails a higher prevalence of classic cardiovascular (CV) risk factors, such as abdominal obesity, impaired glucose tolerance, type 2 diabetes, dyslipidemia, hypertension, and metabolic syndrome in patients with PCOS.³,⁴ Numerous studies have suggested
that subclinical vascular disease is more frequent among women with PCOS compared with controls matched for age and body mass index (BMI). Endothelial dysfunction in women with PCOS, expressed by abnormal flow-mediated dilation (FMD) of the brachial artery, has been reported. Higher serum concentrations of biochemical inflammatory and thrombotic CV risk factors are observed in patients with PCOS. The soluble intercellular adhesion molecule 1 (sICAM-1), soluble vascular cell adhesion molecule 1 (sVCAM-1), and soluble endothelial-leukocyte adhesion molecule 1 (sE-selectin) are considered as biomarkers of CV diseases, also in women with PCOS. PCOS is associated with increased sympathetic tone and higher prevalence of early markers of atherosclerosis, such as greater carotid intima–media thickness (CIMT), arterial stiffness, and coronary artery calcification in later life. Nevertheless, there is no unequivocal evidence for increased CV morbidity and mortality rates in women with PCOS, due to the lack of prospective follow-up studies.

Patients with T1DM are treated with intensive insulin therapy with exogenous insulin administered subcutaneously. To achieve appropriate metabolic control and avoid long-term complications, insulin doses might be supraphysiological. However, new technologies such as continuous subcutaneous insulin infusion allow to reduce the dose of insulin and mimic physiological pancreatic insulin secretion, especially during pregnancy. It has been suggested that exogenous systemic hyperinsulinism may be involved in the pathogenesis of PCOS in women with T1DM. Insulin acts as a gonadotropin, affecting ovarian morphology and function, especially androgen secretion. Insulin has been proved to enhance the effect of luteinizing hormone on theca cells, thus increasing androgen secretion.

It has been reported that the prevalence of PCOS in adult women with T1DM is significantly higher than in controls and reaches 40%, according to the Rotterdam diagnostic criteria. Despite limited evidence, PCOS appears to be among the most common endocrine disorders in women of reproductive age with T1DM. Patients with T1DM also have an increased risk of endothelial dysfunction, premature atherosclerosis, and CV diseases. CIMT and parameters of arterial stiffness in this group of patients are significantly higher in comparison with controls, especially when diabetic complications are present.

So far, there have been no studies regarding the assessment of subclinical markers of atherosclerosis in patients with PCOS and T1DM. Therefore, the aim of our study was to evaluate whether the CV risks conferred by T1DM and PCOS are additive. To answer this question, we focused on early markers of atherosclerosis: measurement of the adhesion molecules sICAM-1 and sE-selectin, as well as the assessment of CIMT and FMD, in the group of women with T1DM and PCOS, compared with women with PCOS only, women with T1DM without PCOS, and healthy women.

**Patients and Methods**

**Patients** We studied 78 women (mean [SD] age, 25 [4.5] years): 19 women with PCOS and T1DM (T1DM+PCOS), 16 women with T1DM without PCOS (T1DM/no-PCOS), 27 women with PCOS only (PCOS), and 16 healthy women (control) matched for age and BMI. Patients with T1DM were recruited from diabetes outpatient clinics in Białystok and from the Department of Endocrinology, Diabetology and Internal Medicine of the Medical University of Białystok. Patients with PCOS attended the endocrinology and gynecology clinics or the Department of Endocrinology, Diabetology and Internal Medicine of the Medical University of Białystok.

The mean (SD) diabetes duration in women with T1DM (35 women) was 11 (6.4) years. Sixteen diabetic women (46%) were treated with intermediate- or long-acting insulin (glargine, detemir) with rapid-acting insulin analogues in multiple daily injections. Nineteen diabetic women (54%) were treated with continuous subcutaneous insulin infusion. Data including age at the onset of diabetes, daily insulin requirements for the last 3 days, glycated hemoglobin A1c (HbA1c) were obtained.

In the T1DM+PCOS group, T1DM developed before menarche in 9 women, 6 of whom presented menstrual disturbances; in the remaining 10 women, T1DM began after menarche and 4 of them complained of menstrual disorders. Among women in the T1DM+PCOS group with diabetes onset before menarche, 4 women complained of oligomenorrhea (1 of them presented polycystic ovarian morphology and 3 of them—both polycystic ovarian morphology and hyperandrogenism), and 2 women complained of amenorrhea (1 of them presented polycystic ovarian morphology and the other one—both polycystic ovarian morphology and hyperandrogenism). The presence of diabetic complications and CV diseases was assessed on the basis of medical history. In the T1DM+PCOS group, 4 women had neuropathy, 1 had nephropathy, 1 had neuropathy and retinopathy, and 1 had nephropathy and retinopathy. In the T1DM/no-PCOS group, 2 women had neuropathy and 1 had nephropathy and retinopathy.

PCOS was diagnosed according to the Rotterdam criteria. In particular, it was defined by the presence of at least 2 of the 3 criteria: oligo- or amenorrhea, clinical and/or biochemical hyperandrogenism, and polycystic ovaries on ultrasonography (>12 follicles of 2 to 9 mm in diameter or ovarian volume exceeding 10 ml in at least 1 ovary). The exclusion criteria, apart from the previously described, were HbA1c over 10%, fasting glycemia exceeding 200 mg/dl, type 2 diabetes, abnormal thyroid function, hyperprolactinemia, late-onset congenital adrenal hyperplasia, use of medications known to affect sex steroids or sex hormone-binding globulin (SHBG), use
of insulin-sensitizing drugs and oral contraceptives in the last 3 months, pregnancy in the last 12 months, and malnutrition. All the participants were Caucasians. None of the women manifested infection symptoms on the day of investigations. The study was approved by the Ethics Committee of the Medical University of Białystok. All participants gave written informed consent after full explanation of the purpose and nature of all procedures used.

**Anthropometric measurements** Physical examination of all participating women was performed. Clinical hyperandrogenism was assessed using the modified Ferriman–Gallwey score for hirsutism (more than 8 points were considered as clinical hyperandrogenism) or on the basis of the presence of acne or androgenic alopecia. Oligomenorrhea or amenorrhea was considered when women had fewer than 6 mestres during the previous year. Height was measured with a Harpenden Stadiometer (Tanita, Tokyo, Japan) to 0.1 cm. Weight and percentage of body fat mass were assessed by bioelectric impedance analysis using the InBody 220 Body Composition Analyzer (InBody Co., Seoul, Korea). Waist circumference was measured using a flexible tape at the narrowest circumference between the lower costal margin and the iliac crest in the standing position. The hip circumference measurement was obtained at the maximum perimeter at the level of the femoral trochanters. BMI and waist-to-hip ratio (WHR) were calculated. Systolic and diastolic blood pressure was measured with an electronic sphygmomanometer in every patient in a relaxed sitting position.

**Ultrasound measurements** Transvaginal ultrasound scans were performed for all patients by the same gynecologist, with a 5- to 9-MHz transvaginal transducer (Voluson 730 Expert, GE Healthcare, Zipf, Austria) in the early follicular phase of the menstrual cycle or any day in women with amenorrhea. PCOS was identified if there were 12 or more follicles of 2 to 9 mm in diameter in an ovary and/or the presence of an enlarged ovary (>10 cm²). The ovarian volume, follicle number, and mean follicle diameter in the right and left ovaries were calculated and summarized for both ovaries.

The brachial and carotid arteries were examined in every patient by the same ultrasonographer, using previously described protocols, with slight modifications.24–26 Philips SONOS 4500 (Philips Medical Systems, Andover, Massachusetts, United States) with a 7.5-MHz linear transducer was used. The CIMT was measured in the right and left common carotid arteries at the distance of more than 1 cm from the bifurcation—3 times on each side. The measurement included end-diastolic estimation of the far walls—the distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line. Analyses were based on the mean value of all the 6 measurements. Ultrasound examination of the right brachial artery was performed in longitudinal sections 2 to 10 cm above the elbow, to observe vasodilation by increased postischemic blood flow. First, brachial artery images were captured 3 times before occlusion. The pneumatic cuff was placed on the right forearm and inflated to the pressure of 210 mm Hg for 3 minutes. The 3 postischemic scans were performed 45 to 60 seconds after rapid pressure release, during reactive hyperemia. FMD was presented as a percentage change of the brachial artery diameter from baseline to the time after ischemia.

**Laboratory analyses** After overnight fasting, morning blood samples were obtained either during the follicular phase (3–7 days) or independently of the cycle phase in the presence of amenorrhea. In both the PCOS and control groups, diabetes was excluded with an oral glucose tolerance test. Fasting serum glucose and insulin levels, hormonal profile, lipid profile, and HbA₁c, sE-selectin, and sICAM-1 levels were estimated. All blood samples for glucose and insulin levels were collected at baseline and at 30, 60, 90, and 120 minutes of the oral glucose tolerance test.

Serum glucose levels were measured by an enzymatic reference method with hexokinase (Cobas c111, Roche Diagnostic Ltd., Rotkreuz, Switzerland). Serum insulin concentrations were assayed by the immunoradiometric method (DIASource ImmunoAssays S.A., Ottignies-Louvain-la-Neuve, Belgium). The HbA₁c level was measured using high-performance liquid chromatography (Bio Rad, Hercules, California, United States). Concentrations of total cholesterol, high-density lipoprotein cholesterol, and triglycerides were determined by an enzymatic colorimetric method (Cobas c111, Roche Diagnostic Ltd., Rotkreuz, Switzerland). Low-density lipoprotein cholesterol concentrations were calculated by the Friedewald equation. High-sensitivity C-reactive protein (hs-CRP) levels were measured by a highly sensitive immunoturbidimetric assay (Cobas c111, Roche Diagnostic Ltd.). The serum levels of luteinizing hormone and follicle-stimulating hormone were detected by immunoradiometric assays (DIASource ImmunoAssays S.A., where-as the serum testosterone level was estimated by a radioimmunoassay (DIASource ImmunoAssays S.A.). The free androgen index was calculated as serum testosterone (nmol/l) × 100/SHBG (nmol/l) ratio.27 sE-selectin and sICAM-1 were detected by enzyme-linked immunosorbent assays using commercially available reagents (R&D Systems Inc., Minneapolis, Minnesota, United States). The minimum detectable concentration was 0.049 ng/ml for sICAM-1 and 0.003 ng/ml for sE-selectin. The intraassay and interassay coefficients of variation for sICAM-1 were below 5% and 6.7%, respectively, and for sE-selectin—below 6.9% and 8.6%, respectively.

**Statistical analysis** Statistical analysis was performed using the Statistica 12.5 package (Statsoft
TABLE 1  Clinical characteristics of the study groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>T1DM + PCOS (n = 19)</th>
<th>PCOS (n = 27)</th>
<th>T1DM/no-PCOS (n = 16)</th>
<th>Control (n = 16)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>24.0 (22.0–28.0)</td>
<td>24.0 (22.0–27.0)</td>
<td>26.5 (21.0–31.5)</td>
<td>23.5 (21.5–27.5)</td>
<td>0.659</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.20 (22.20–26.40)</td>
<td>24.8 (21.8–28.6)</td>
<td>24.4 (22.2–27.9)</td>
<td>21.8 (21.4–23.6)</td>
<td>0.208</td>
</tr>
<tr>
<td>WHR</td>
<td>0.82 (0.79–0.86)</td>
<td>0.84 (0.79–0.87)</td>
<td>0.83 (0.81–0.86)</td>
<td>0.79 (0.77–0.83)</td>
<td>0.148</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>30.4 (26.3–36.6)</td>
<td>30.8 (26.4–38.4)</td>
<td>29.8 (22.3–34.6)</td>
<td>27.0 (22.8–35.7)</td>
<td>0.670</td>
</tr>
<tr>
<td>Ferriman–Gallwey score</td>
<td>3.0 (2.0–5.0)</td>
<td>7.0 (3.0–12.0)</td>
<td>2.0 (1.0–3.0)</td>
<td>3.0 (2.0–5.5)</td>
<td>0.009</td>
</tr>
<tr>
<td>Age at diabetes diagnosis, y</td>
<td>12.5 (11.0–15.0)</td>
<td>–</td>
<td>17.0 (9.5–20.5)</td>
<td>–</td>
<td>0.147</td>
</tr>
<tr>
<td>Diabetes duration, y</td>
<td>10.0 (9.0–13.0)</td>
<td>–</td>
<td>8.0 (4.0–15.5)</td>
<td>–</td>
<td>0.417</td>
</tr>
<tr>
<td>HbaA1c, %</td>
<td>6.8 (6.5–8.0)</td>
<td>–</td>
<td>8.1 (6.8–8.9)</td>
<td>–</td>
<td>0.185</td>
</tr>
<tr>
<td>Insulin dose, U/kg</td>
<td>0.56 (0.47–0.80)</td>
<td>–</td>
<td>0.60 (0.44–0.71)</td>
<td>–</td>
<td>0.835</td>
</tr>
<tr>
<td>Daily insulin dose, U/24 h</td>
<td>41.0 (32.0–50.0)</td>
<td>–</td>
<td>45.5 (28.5–55.5)</td>
<td>–</td>
<td>0.959</td>
</tr>
</tbody>
</table>

Data are presented as median (interquartile range). Significant differences:

a  PCOS vs T1DM/no-PCOS

Abbreviations: BMI, body mass index; HbaA1c, glycated hemoglobin A1c; PCOS, polycystic ovary syndrome; T1DM, type 1 diabetes mellitus; WHR, waist-to-hip ratio.

The clinical characteristics of the study groups are presented in TABLE 1. No significant differences in anthropometric measurements were observed between the groups. Age at diabetes diagnosis, diabetes duration, HbaA1c levels, and daily insulin requirements were comparable between women with T1DM+PCOS and those with T1DM/no-PCOS (TABLE 1).

Serum testosterone concentrations were higher in the T1DM+PCOS and PCOS groups, as compared with the control group (P = 0.002 and P = 0.014, respectively). SHBG concentrations were lower in patients with PCOS, as compared with the T1DM+PCOS group (P = 0.045) (TABLE 2).

The PCOS and T1DM+PCOS groups were comparable in terms of ovarian volume and ovarian follicle number on ultrasound. The latter was higher in the T1DM+PCOS and PCOS groups than in the control group (P = 0.044 and P = 0.038, respectively), as well as in the T1DM+PCOS group compared with the T1DM/no-PCOS group (P = 0.001) (TABLE 2). The most prevalent phenotype of PCOS in the T1DM+PCOS group was hyperandrogenism and polycystic ovaries, while in the PCOS group, it was hyperandrogenism and ovulatory disorders.

The highest concentrations of sICAM-1 and sE-selectin were found in the groups with T1DM (PCOS+T1DM, T1DM/no-PCOS), with no significant differences between the groups. Serum concentrations of sICAM-1 were higher in the T1DM+PCOS and T1DM/no-PCOS groups, compared with patients with PCOS only (P = 0.041 and P = 0.007, respectively). Similarly, the T1DM+PCOS and T1DM/no-PCOS groups showed higher concentrations of sE-selectin than women with PCOS only (P = 0.002 and P < 0.001, respectively) (TABLE 3). CIMT and brachial FMD were not significantly different between the groups (TABLE 3).

In patients with T1DM (with and without PCOS), positive correlations were found between sICAM-1 concentrations and BMI (r = 0.34, P = 0.047) and fat mass (r = 0.38, P = 0.033). CIMT showed a positive correlation with patient’s age (r = 0.37, P = 0.039) and daily insulin dose (r = 0.37, P = 0.039). FMD was negatively correlated with diabetes duration (r = –0.42, P = 0.02) (TABLE 4).

In the T1DM+PCOS group, serum sE-selectin concentrations correlated positively with systolic blood pressure (r = 0.51, P = 0.025), CIMT was correlated with daily insulin dose (r = 0.51, P = 0.046), and FMD, with patient’s age (r = –0.51, P = 0.035) and SHBG concentrations (r = –0.54, P = 0.031).

In the whole study group, sICAM-1 levels showed positive correlations with BMI (r = 0.4, P < 0.001), WHR (r = 0.33, P = 0.003), and fat mass (r = 0.39, P < 0.001). Serum sE-selectin levels correlated positively with BMI (r = 0.28, P = 0.015) and WHR (r = 0.33, P = 0.003). Data are presented in TABLE 5. In the multivariable logistic regression model, the presence of T1DM, adjusted for sICAM-1 levels, was the only predictor of sE-selectin levels in the whole study group (odds ratio, 8.03; 95% confidence interval, 2.56–13.49; P = 0.005).
In this study, we demonstrated that serum sE-selectin and sICAM-1 levels did not differ between young normal-weight women with T1DM and PCOS and those with T1DM without PCOS and that the levels were significantly higher in women with PCOS and T1DM than in those with PCOS without T1DM, despite comparable parameters of endothelial function: FMD and CIMT. There is evidence for increased CV risk in women only with PCOS or only with T1DM. However, to date, none of the investigators have examined the group of women with coexistent PCOS and T1DM. In this study, we assessed women of reproductive age, affected by both diseases.

**DISCUSSION**

Available studies confirmed that T1DM and PCOS are important risk factors for atherogenesis and vascular complications. The activation of adhesion molecules precedes vascular...
TABLE 5  Correlations of adhesion molecule concentrations with selected clinical characteristics in the whole study group (n = 78)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>sE-selectin</th>
<th>sICAM-1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>P value</td>
</tr>
<tr>
<td>BMI</td>
<td>0.280</td>
<td>0.015</td>
</tr>
<tr>
<td>WHR</td>
<td>0.334</td>
<td>0.003</td>
</tr>
<tr>
<td>Fat mass</td>
<td>0.180</td>
<td>0.126</td>
</tr>
<tr>
<td>CRP</td>
<td>0.274</td>
<td>0.022</td>
</tr>
<tr>
<td>CIMT</td>
<td>0.332</td>
<td>0.005</td>
</tr>
<tr>
<td>FMD</td>
<td>0.132</td>
<td>0.274</td>
</tr>
</tbody>
</table>

Abbreviations: see TABLES 1, 2, and 3

complications, leading to progression of atherosclerosis. It has been demonstrated that young patients with T1DM and poor metabolic control had higher serum concentrations of sICAM-1, which correlated positively with circulating endothelial progenitor cells. Soedamah-Muthu et al showed that sVCAM-1 and sE-selectin levels were associated with microvascular and macrovascular complications. In the EURODIAB Prospective Complications Study, the serum levels of adhesion molecules in patients with T1DM were strongly and independently associated with inflammatory markers.

So far, there have been no studies investigating CV risk in women with T1DM and PCOS. In a recent meta-analysis, Escobar-Morreale et al reported that the development of full PCOS phenotype with its symptoms in girls with T1DM is probably a long-term process. Thus, cardiometabolic consequences are observed later in life, and prospective studies are required to further investigate this issue.

There have been numerous studies reporting an increased CV risk in women with T1DM and PCOS. Obesity, dyslipidemia, chronic low-grade inflammatory state, and insulin resistance are associated with the development of CV risk factors. Diamanti-Kandarakis et al observed that in PCOS the elevated serum concentrations of sICAM-1, sVCAM-1, endothelin 1, and CRP were correlated with lower FMD. PCOS and BMI were reported as predictors of increased concentrations of sE-selectin and sICAM-1. Administration of metformin in women with PCOS significantly reduced hs-CRP and sVCAM-1 concentrations, suggesting that chronic low-grade inflammation is a proatherogenic state. The phenotypic variability of PCOS is also important. The phenotypes which include ovulatory disorders and hyperandrogenism appear to have the most negative impact on CV risk.

In our study, we did not find differences in hs-CRP concentrations between the groups; however, in the whole study group, there were significant positive correlations between sE-selectin, sICAM-1, and hs-CRP levels, confirming the previous data. The expression of adhesion molecules is also affected by other factors, such as dyslipidemia or hyperglycemia. In our study, the lipid profile did not differ between the groups. In the PCOS and control groups, diabetes and prediabetes were excluded. In the T1DM+PCOS group, metabolic control was satisfying. However, it is worth mentioning that earlier long-term poor glycemic control could have affected the studied parameters, which is consistent with the concept of metabolic memory. In a recently published study by Kiec-Wilk et al, the number of hypoglycemic episodes in patients with T1DM treated with continuous subcutaneous insulin infusion was related to the serum levels of adhesion molecules. In our study, HbA1c levels did not differ between the diabetic groups; nevertheless, we cannot exclude the possible effects of hypoglycemic events on the concentrations of adhesion molecules. The phenotype with menstrual disorders and hyperandrogenism, mostly present in our group with PCOS, has the most negative impact on CV risk. Young age, normal weight, and the lack of metabolic abnormalities probably explain our findings in women with PCOS.

In the T1DM+PCOS group, the effect of the phenotype—hyperandrogenism and polycystic ovaries—has not been explained and requires further studies. Considering that elevated serum concentrations of sICAM-1 and sE-selectin were observed in both groups with T1DM, the presence of PCOS in these women is probably not the additive factor.

Despite the increased concentrations of adhesion molecules, we did not demonstrate the differences in FMD and CIMT among the studied women. The possible explanation is normal weight and young age of the studied groups matched for BMI. Similarly, Arikan et al investigated young, lean women with PCOS whose FMD was comparable to that in the control group, despite the presence of insulin resistance. Additionally, Mather et al reported normal endothelial function in patients with PCOS with obesity and insulin resistance. On the contrary, there is evidence that the presence of obesity and insulin resistance in PCOS may affect endothelial function. In the DCCT/EDIC study, Sprung et al, in a meta-analysis of observational studies, confirmed that endothelial dysfunction is inherent in PCOS and that FMD impairment may be affected not by fat mass but by the differences in fat distribution. Contrary to our findings, Ce et al reported lower FMD in 49% of adolescents with T1DM, independent of age, smoking, hypertension, or hyperlipidemia. This finding was explained by poor glycemic control and disease duration. In the DCCT/EDIC study, a 12-year follow-up of patients with T1DM showed that individual biomarkers (of acute phase, thrombosis, and endothelial dysfunction) were not associated with subclinical atherosclerosis assessed by the progression of CIMT. A Polish study reported significantly higher CIMT in patients with T1DM with microangiopathy, in comparison with those without this diabetic complication. Moreover, Burchardt et al observed a significant reduction in CIMT in patients with T1DM receiving
adjunctive metformin treatment, in comparison with those treated only with insulin. In our population, we did not observe changes in FMD between the groups, probably due to the small proportion of women with T1DM and diabetic complications. In addition, sex seems to be an important factor. Bruzzi et al 23 reported that boys with T1DM had more profound endothelial dysfunction than girls with T1DM after 1 year of follow-up. Moreover, the different methods of FMD and CIMT assessment in various centers may lead to difficulties in comparing results. Importantly, in our study, despite normal CIMT, we found a positive correlation of this parameter with age and daily insulin dose in all women with T1DM. We also confirmed the impact of diabetes duration on FMD.

This is the first study comparing the serum concentrations of sICAM-1 and sE-selectin, as well as parameters of endothelial function (FMD) and early structural vascular changes (CIMT) in the 4 groups: T1DM+PCOS, T1DM/no-PCOS, PCOS, and healthy women, matched for age and BMI. Our main finding is the increased serum concentration of sE-selectin and sICAM-1 without evidence of functional and structural vascular changes, demonstrated only in women with T1DM, with and without PCOS. Despite the young age, a relatively short diabetes duration, and metabolic control, the effect of T1DM on the activation of adhesion molecules seems to be strong. Thereby, it is an early process without evidence of vascular changes. A different phenotype of PCOS that develops in these women is probably not the additive factor. However, a longer follow-up is needed to confirm our results.

In summary, the highest serum concentrations of sICAM-1 and sE-selectin were observed in women with T1DM. No significant differences were found between the groups of women with T1DM and PCOS and those with T1DM without PCOS. Whether PCOS affects CV risk in women with T1DM in later life requires further study.

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Contribution statement AL contributed to the concept and design of the study, acquisition of data, statistical analysis and interpretation of data, writing the article, and final approval of the version to be submitted; AA and MJ contributed to acquisition of data, revising the article, and final approval of the version to be submitted; JT, AK, JH, and ML contributed to acquisition of data and final approval of the version to be submitted; MG and AB contributed to participation in the design of the study, revising the article, and final approval of the version to be submitted; IK contributed to the concept and design of the study, statistical analysis and interpretation of data, writing the article, and final approval of the version to be submitted.

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