Cardiovascular Diabetology

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Preeclampsia as an independent predictor of atherosclerosis progression in women with type 1 diabetes: a 5-year prospective study

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Abstract

Background Preeclampsia (PE) and type 1 diabetes (T1D) are significant risk factors for cardiovascular disease (CVD), but their combined effect on atherosclerosis progression has not been fully explored. This study aimed to evaluate the impact of T1D and PE on the progression of atherosclerosis.

Methods Prospective cohort study of 112 women divided into four groups: T1D + /PE + (n = 28), T1D + /PE– (n = 28), T1D–/PE + (n = 28), and T1D–/PE– (n = 28). Participants underwent an initial assessment and a follow-up visit five years later, which included anthropometric evaluation, blood tests, and carotid ultrasound. Atherosclerosis progression was defined as an increase in carotid plaque number or the occurrence of a cardiovascular event (CVE) during follow-up (fatal or non-fatal ischemic heart disease, fatal or non-fatal stroke, and/or heart failure).

Results A total of 104 women (92.9%) completed the follow-up (54 with T1D, mean age at inclusion 45.2 ± 7.6 years, mean follow-up 5.3 ± 1.2 years). An increase in carotid plaques was identified in 34 women (32.7%), and 3 CVEs (2.9%) occurred. In women with T1D, a history of PE was associated with a twofold increase in atherosclerosis progression (57.7% vs 25.0%, p = 0.015). In multivariate models adjusted for age, T1D and cardiovascular risk factors, PE [OR 4.97 (1.61–15.29), p = 0.005] and PE + T1D [OR 7.69 (1.25–47.29), p = 0.028] were independently associated with atherosclerosis progression.

Conclusions PE was a strong independent predictor of atherosclerosis progression over a 5-year follow-up period, with an additive effect in T1D. These findings highlight preeclampsia as a significant CVD risk enhancer in young women with T1D.

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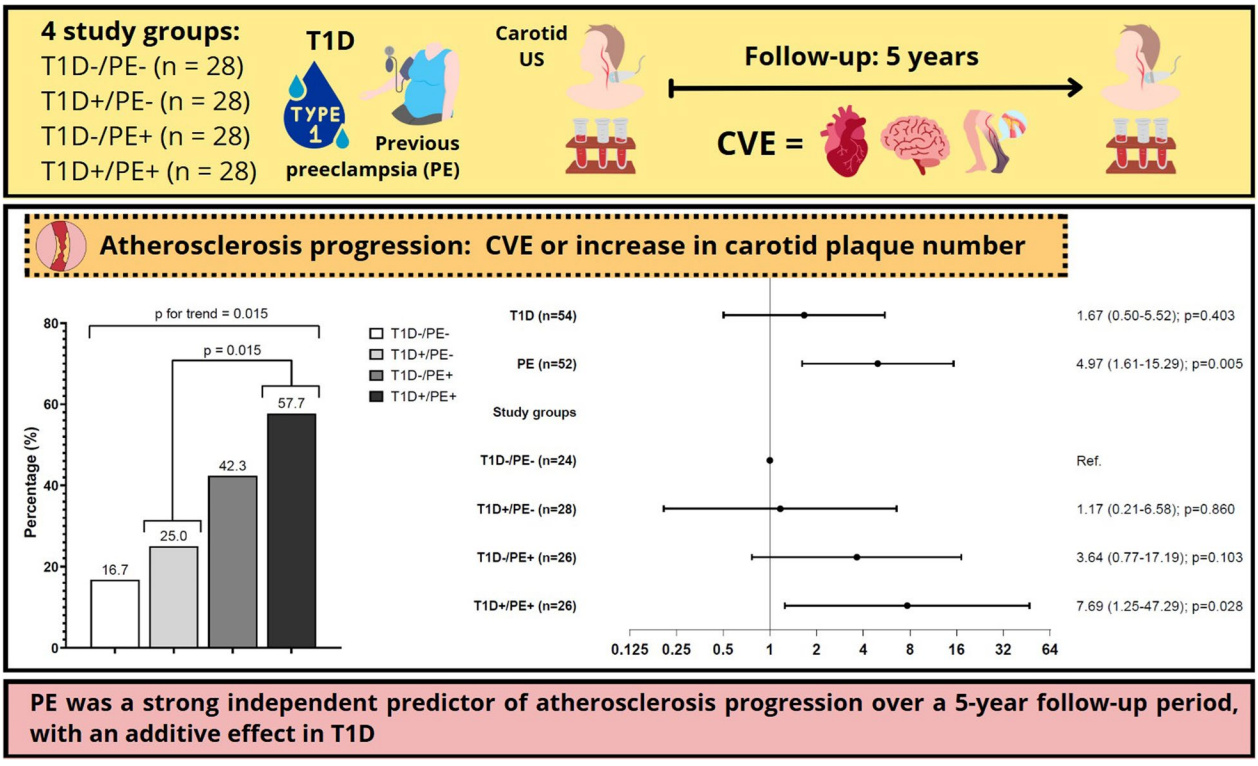
Graphical abstract



Research insights

What is currently known about this topic? Women with type 1 diabetes (T1D) experience twice the excess risk of cardiovascular events compared to men, relative to individuals without T1D. Women with T1D have a higher prevalence of preeclampsia, an independent sex-specific cardiovascular risk factor. In a previous study, a history of preeclampsia was associated with preclinical atherosclerosis in women with T1D, but its independent relationship with atherosclerosis progression remains unexplored.

What is the key research question? Does previous preeclampsia independently predict atherosclerosis progression in women with T1D over a 5-year follow-up period?

What is new? Preeclampsia is a strong independent predictor of atherosclerosis progression in women with T1D. Women with both T1D and preeclampsia have twice the rate of atherosclerosis progression compared to those with T1D alone.Preeclampsia and T1D have an additive effect on atherosclerosis progression, even after adjusting for main cardiovascular risk factors.

How might this study influence clinical practice? This study suggests that a history of preeclampsia should be considered a risk-enhancing factor in cardiovascular risk assessments for women with T1D, potentially leading to more intensive prevention strategies.

Keywords Preeclampsia, Type 1 diabetes, Gender, Cardiovascular disease

Background

Mortality among people living with type 1 diabetes (T1D) has decreased in recent years, yet their risk of death remains two to five times higher than in people without diabetes [1]. Although tight glycemic control reduces cardiovascular disease (CVD) risk, the leading cause of death in this population, a significant excess cardiovascular mortality persists, even among those achieving glycemic targets [2]. This excess CVD risk is particularly pronounced in women, who face roughly twice the excess risk of cardiovascular events (CVE) than men, relative to their counterparts without T1D [3, 4]. These disparities are especially significant in women with early-onset T1D, resulting in a considerable reduction in life expectancy—approximately 18 years for women compared to 14 years for men [5].

Unlike men, women encounter unique cardiovascular risk factors (CVRF) related to reproductive health that warrant consideration. Hypertensive pregnancy disorders, particularly preeclampsia, trigger oxidative stress and an inflammatory response that may persist after pregnancy, contributing to long-term vascular dysfunction and dysregulated lipid metabolism. Preeclampsia has not only been consistently linked to markers of vascular damage and preclinical atherosclerosis [6–8], but has also been shown in epidemiological studies to independently predict future CVD, even after adjusting for traditional CVRF [9, 10]. Consequently, international CVD prevention guidelines now recommend including preeclampsia as a risk-enhancing factor in cardiovascular risk assessments for the general population [11, 12]. However, despite evidence indicating that women with T1D are at a heightened risk of preeclampsia [13], current CVD guidelines for T1D [14, 15] do not address this factor, nor is it included in specific CVD risk scales [16, 17].

In a previous study, our group reported that a history of preeclampsia was associated with preclinical carotid atherosclerosis in women, both with and without T1D [18]. Preeclampsia appeared to have a similar impact on preclinical atherosclerosis as T1D, with both conditions exerting an additive effect. Supporting this, a recent Swedish study also reported that a history of hypertensive disorders of pregnancy increased the risk of incident CVD by 20% in women with T1D, although this association lost significance in fully adjusted models [19]. Building on this evidence, the current study aims to further evaluate the independent contribution of preeclampsia to atherosclerosis progression, defined as either the occurrence of a CVE or an increase in the number of carotid plaques, in women with T1D over a 5-year follow-up period.

Methods

Subjects

This prospective study is a follow-up to a previous investigation, and full details of the selection criteria and design of baseline investigations have been published elsewhere [18]. Briefly, women without previous CVD, whose last pregnancy occurred at least five years before, were recruited and divided into 4 groups (n = 28 per group): (1) T1D with previous preeclampsia (T1D + /PE +); (2) T1D without history of preeclampsia (T1D + /PE); (3) history of preeclampsia without diabetes (T1D−/PE +); and (4) a control group with neither T1D nor preeclampsia (T1D−/PE−). Diagnoses of T1D and preeclampsia were made according to internationally recommended criteria [20, 21].

The participants from the T1D + /PE + group were selected from the outpatient clinics of each institution. Each patient included in this group was matched by age (± 3 years), body mass index (BMI; ± 3 kg/m^2) and smoking habit (former and current smokers) with 3 participants to form the remaining groups. Groups including T1D participants were further matched by diabetes duration (± 3 years) and the presence of diabetic retinopathy (DR). When multiple potential matches were identified, those with the time since the last pregnancy closest to the individual from the T1D + /PE + group were selected.

The study protocol was developed in accordance with the principles of the Declaration of Helsinki and received approval from the hospital Research Ethics Committees. All participants provided written informed consent.

Clinical and laboratory measures

All participants attended an initial visit for a physical examination and verification of inclusion and exclusion criteria. Demographic and clinical data were collected, including family history of premature CVD in first-degree relatives, smoking status (current, former, or never smoker), presence of hypertension, and current pharmacotherapy. Diabetes duration and current insulin therapy (continuous subcutaneous insulin infusion or multiple-dose insulin regimen) were extracted from medical records.

Anthropometric measurements were obtained as follows: participants were weighed in light clothing without shoes, using calibrated scales accurate to the nearest 0.1 kg. Height was measured to the nearest 0.5 cm. BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Waist circumference was measured to the nearest 0.5 cm with an anthropometric tape positioned midway between the lowest rib and the iliac crest, during minimal respiration. Blood pressure was recorded using an Omron HEM-7223-E monitor (Hoofddorp, The Netherlands) following several minutes of rest.

Laboratory parameters were measured in fasting blood and first-morning urine spot samples. Serum creatinine, glucose, lipid profile (including total cholesterol, triglycerides, and HDL-cholesterol) and the urinary albumin-to-creatinine ratio were determined using standardized assays. LDL-cholesterol was determined by the Friedewald formula. Glomerular filtration rate was estimated using the Chronic Kidney Disease-Epidemiology Collaboration equation (CKD-EPI). HbA1c was measured centrally by high-performance liquid chromatography and expressed in National Glycohemoglobin Standardization Program/Diabetes Control and Complications Trial units.

Diabetic kidney disease (DKD) was defined as an albumin-to-creatinine ratio ≥ 30 mg/g and/or an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m2. The use of angiotension-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB), without

a history of hypertension or CVD, was also considered as DKD. DR was diagnosed using non-mydriatic retinography, confirmed by an ophthalmologist. Hypertension was defined as consecutive clinical measurements of systolic blood pressure ≥ 140 mmHg and diastolic blood pressure ≥ 90 mmHg, or current treatment with antihypertensive drugs, excluding ACEi/ARB prescribed specifically for DKD). Finally, in patients with T1D, cardiovascular risk was assessed with Steno T1 Risk Engine (ST1RE)[16] which estimates the 10-year risk of fatal or nonfatal CVD based on 10 variables: age, sex, diabetes duration, HbA1c, systolic blood pressure, LDL-cholesterol, albuminuria, eGFR, smoking habit, and regular exercise (≥ 3.5 h/week).

Carotid B-mode ultrasound imaging

Bilateral carotid artery ultrasound images were acquired using high-resolution B-mode ultrasound (*Acuson X700* [Siemens Healthineers] in Hospital Clínic de Barcelona and *Logic P9* [General Electrics] in Hospital Mútua de Terrassa). Standardized imaging protocols to evaluate carotid intima-media thickness (IMT) and the presence of plaques were followed, as previously described [22].

Carotid images visualized using B-mode and color Doppler in both longitudinal and transverse planes to evaluate the presence of circumferential asymmetry. Carotid plaques were defined as focal echo-structures protruding into the arterial lumen by at least 50% of the surrounding IMT or when IMT was at least 1.5 mm, measured from the media-adventitia interface to the intima-lumen surface [23]. The mean and mean maximum IMT of all carotid segments (common carotid, bulb, and internal carotid) were recorded, along with the maximum height of carotid plaques. If plaques were present, the maximum IMT was defined as the height of the highest carotid plaque. IMTs were measured offline by semiautomatic software by the same experienced researcher (A.J.A), who was blinded to the status of each patient.

Follow-up assessment and outcomes

All participants were recalled for a follow-up assessment 4–6 years later, where they underwent the same evaluation as in the baseline assessment, including clinical and laboratory measures. Following European guidelines on the use of carotid ultrasonography [11], carotid B-mode ultrasound imaging to detect preclinical carotid atherosclerosis was also performed in the absence of a CVE during the follow-up period. The ultrasonographer was blinded to the participants' history of preeclampsia. CVE occurrence was defined as a documented medical history of new-onset ischemic heart disease, stroke, or heart failure. The 5-year timeframe was chosen to allow sufficient time to observe meaningful changes in carotid plaque burden or the occurrence of CVE.

The primary outcome of the study was the progression of atherosclerosis, defined as either the occurrence of a CVE or an increase in the number of carotid plaques at the follow-up assessment.

Statistical analyses

All clinical data were deposited in the Research Electronic Data Capture (REDCap) database. Participants with missing data for key variables were excluded from analyses. No imputation methods were applied as missing data were minimal (< 5% for all variables). Data are presented as mean ± standard deviation, median and 25th and 75th percentiles or number (percentage). For continuous variables, normality was assessed using a Kolmogorov–Smirnov test.

Comparisons of variables according to the presence of atherosclerosis progression were performed using an unpaired Student's t-test for normally distributed variables, or the Mann–Whitney U test for non-normally distributed variables, as appropriate. The Kruskal–Wallis, Pearson's chi-squared test and ANOVA were performed, as appropriate, for comparisons between study groups (T1D−/PE−; T1D−/PE +; T1D + /PE−, and T1D + / PE +). The Bonferroni test was used as a post hoc analysis to make pairwise comparisons, correcting for multiple analyses.

To explore independent associations between T1D and/or preeclampsia with atherosclerosis progression (defined as either an increase in the number of carotid plaques or the occurrence of a CVE), logistic binary regression models were developed. The first model included age at baseline, preeclampsia, T1D, center and time since initial visit as covariates. The second model included the same variables as above, in addition to main variables associated with atherosclerosis progression (systolic blood pressure [SBP], BMI, and presence of menopause at baseline). A third model included model 2 plus other CVD risk factors at baseline (LDL-cholesterol, active smoking habit, and serum creatinine), and statin exposure (statin score; see details below) at the follow-up visit. Additionally, the same models were applied to assess the independent relationship between the study groups (T1D−/PE−; T1D−/PE +; T1D + /PE−, and T1D + / PE +) and atherosclerosis progression. As an exploratory analysis, we further included HbA1c in logistic regression models in participants with T1D, while maintaining adjustments for all covariates included in Model 3. Finally, to assess the robustness of our primary findings, we performed three sensitivity analyses: (1) exclusion of participants with CVE during follow-up; (2) exclusion of those with baseline DKD; (3) exclusion of statin-treated participants at baseline.

Since many subjects were treated with lipid-lowering drugs, which may induce regression of IMT and plaques, we adjusted for statin treatment when evaluating

associations with atherosclerosis. A statin score, an estimation of lifetime exposure to cholesterol-lowering treatment, was calculated for each participant as the product of the duration of treatment (in years) and the average statin dose received (standardized to simvastatin in mg/day) [24].

At the time the study was designed, there was no available data on differences in IMT or plaque presence between individuals with T1D with and without previous preeclampsia. As a result, the sample size was estimated using existing data on common carotid artery IMT comparisons between women with and without a history of preeclampsia [25, 26]. Assuming a true mean difference of 0.08 mm (with a standard deviation of 0.10) in CCA-IMT between patients with T1D with and without previous preeclampsia, it was calculated that 26 participants per group would be required to detect such differences. This calculation was based on a type I error rate of 0.05 and a statistical power of 80%.

IBM SPSS Statistics version 23.0 (SPSS Inc.; Chicago, IL, USA) was used to perform the statistical analyses. All tests were two-tailed and significance was considered if p-value < 0.05.

Results

Subjects' characteristics

A total of 112 patients who met the inclusion criteria were enrolled and followed for a mean period of 5.3 ± 1.2 years. Of these, 8 patients were lost to follow-up: 2 from the T1D + /PE + group, 2 from the T1D−/PE + group, and 4 from the T1D−/PE− group (Supplementary Fig. 1). Nevertheless, cardiovascular status on medical records was available for all of them, and none experienced a CVE during the follow-up period.

The mean age of analyzed participants (n = 104) was 45.2 ± 7.6 years and all of them were Caucasian. At baseline, the prevalence of carotid atherosclerosis (defined as ≥ 1 plaque) was 22.1% (n = 23), with no significant differences among groups (p = 0.247; Table 1). Menopause was present in 22.1% (n = 23) of participants, with no significant group differences, and none had undergone past or current hormone replacement therapy. Hypertension was present in 15.4% (n = 16) and differences among groups were observed (p = 0.007), with highest prevalence in participants with both preeclampsia and T1D (Table 1). No significant differences were observed in age and other CVRF (smoking habit, BMI, and waist circumference) among the 4 groups (Table 1).

Regarding participants with T1D, mean diabetes duration was 27.5 ± 7.4 years and median HbA1c 7.6% (7.1–8.4). The prevalence of DKD and DR was 9.3% and 37.0%, respectively. The groups with and without preeclampsia had similar diabetes duration, glycemic control, prevalence of chronic complications, use of cardioprotective drugs and 10-year estimated CVD risk (as assessed by ST1RE) (Table 1). Only small differences in renal function were detected, with higher creatinine levels (0.81 vs 0.69 mg/dL, p = 0.035) and lower eGFR (100 vs 106 mL/min/1.73m^2, p = 0.021) in the group with preeclampsia.

Prevalence of cardiovascular events and preclinical atherosclerosis at the follow-up visit

Characteristics of the study groups at the follow-up visit are provided in Supplementary Table 1. Regarding subjects with T1D, only creatinine levels remained significantly higher in the group with preeclampsia (T1D + PE +; 0.80 vs 0.72 mg/dL, p = 0.038), without other between-group differences (Supplementary Table 1).

During the follow-up period, 2.9% (n = 3) of the subjects experienced a nonfatal CVE (1 ischemic heart disease, 1 stroke, and 1 heart failure). Moreover, preclinical carotid atherosclerosis was detected in 41.6% (n = 42) of the remaining participants at the follow-up visit, with 11.9% harboring ≥ 3 carotid plaques. Overall, atherosclerosis (defined as CVE or ≥ 1 carotid plaque at follow-up) was detected in 43.3% (n = 45) of the sample, while clinical or advanced preclinical atherosclerosis (≥ 3 carotid plaques) was observed in 14.4% (n = 15) of the individuals.

The prevalence of atherosclerosis increased in a stepwise manner according to T1D and preeclampsia status. The lowest prevalence was observed in the control group (T1D−/PE−; 20.8%), followed by the T1D group (T1D + /PE−; 25.0%), the preeclampsia group (T1D−/PE +; 42.3%), and the highest prevalence in those with both conditions (T1D + /PE +; 57.7%) (p for trend = 0.014; p vs T1D + /PE− = 0.015;.. Supplemmentary Fig. 2). A similar trend was observed for clinical or advanced preclinical atherosclerosis (CVE or ≥ 3 carotid plaques), with the group with both conditions showing the highest prevalence (p for trend 0.006; Supplementary Fig. 2).

Predictors of atherosclerosis progression

At the follow-up visit, 35.6% (n = 37) of the participants had experienced atherosclerosis progression, defined as the occurrence of CVE or an increase in the number of carotid plaques. Baseline characteristics, laboratory data, and treatment of the study population stratified by progression status are presented in Table 2. As expected, progressors were older (48.1 ± 7.8 vs 43.6 ± 7.0 years; p = 0.003), had a higher prevalence of hypertension (27.0% vs. 9.0%; p = 0.017), and had a higher SBP (126 ± 16 vs 119 ± 13 mmHg; p = 0.015) and BMI (27.0 ± 5.9 vs 25.0 ± 4.3; p = 0.049). Additionally, menopause (37.8% vs 13.4%; p = 0.004) and presence of ≥ 1 carotid plaque at baseline (37.8% vs 13.4%; p = 0.005) were associated with atherosclerosis progression. For participants with T1D, a longer diabetes duration (31.2 ± 7.3 vs 24.9 ± 6.4 years; p = 0.002) and higher ST1RE scores

Table 1 Basal characteristics of the participants according to the study group

	T1D-/PE– (n = 24)	T1D + /PE– (n = 28)	T1D–/PE + (n = 26)	T1D + /PE + (n = 26)	p-value among groups
Clinical characteristics					
Age (years)	44.5 ± 7.6	45.1 ± 7.9	45.5 ± 7.4	45.7 ± 7.7	0.950
Premature CVD in first-degree relatives* (%)	1 (4.2)	2 (7.1)	7 (26.9)[a]	4 (15.4)	0.076
Current smokers (%)	3 (12.5)	7 (25.0)	5 (19.2)	6 (23.1)	0.698
Hypertension (%)	0 (0)	4 (14.3)[a]	3 (11.5)	9 (34.6)[a]	**0.007**
SBP (mmHg)	116 ± 14	120 ± 16[a,b]	121 ± 13	128 ± 15[a,b]	0.051
DBP (mmHg)	75 ± 8	77 ± 9	80 ± 11	77 ± 10	0.318
BMI (kg/m^2)	25.8 ± 4.9	25.0 ± 4.5	26.7 ± 6.4	25.2 ± 4.0	0.584
Waist circumference (cm)	85.6 ± 12.5	86.1 ± 12.5	88.5 ± 12.0	85.1 ± 11.0	0.758
No. of pregnancies	2 (1–3)	2 (1–2)	2 (1–2)	2 (1–3)	0.571
Menopause	6 (25.0)	5 (17.9)	6 (23.1)	6 (23.1)	0.932
Diabetes-related clinical characteristics					
Diabetes duration (years)	–	27.0 ± 8.8	–	28.1 ± 5.8	0.852
Microvascular complications	–	1 (3.6)	–	4 (15.4)	0.153
Diabetic nephropathy (%)	–	9 (32.1)	–	11 (42.3)	0.312
Diabetic retinopathy (%)					
ST1RE (%)	–	13.4 ± 6.0	–	11.3 ± 6.9	0.291
Laboratory characteristics					
Fasting plasma glucose (mg/dL)	84 (80–89)	129 (90–172) [a,b]	91 (84–95)	149 (110–206) [a,b]	**< 0.001**
HbA1c (%)	5.1 (4.9–5.3)	7.6 (7.0–8.4) [a,b]	5.3 (5.1–5.4)	7.7 (7.2–8.6) [a,b]	**< 0.001**
Serum creatinine (mg/dL)	0.67 ± 0.11	0.69 ± 0.11	0.69 ± 0.08	0.81 ± 0.29 [a,b,c]	**0.010**
eGFR(CKD-EPI; ml/min/1.73m^2)	107 ± 10	106 ± 8	105 ± 7	100 ± 10[a]	**0.023**
Albumin-to-creatinine ratio (mg/g)	4.5 (3.0–7.9)	6.5 (4.0–11.4)	3.8 (2.3–6.3)	7.0 (2.0–16.0)	0.448
Leucocyte count (10^9/L)	6.5 (5.0–7.3)	7.1 (4.9–8.9)	6.0 (4.9–7.6)	6.4 (5.0–7.1)	0.372
Total cholesterol (mg/dL)	105 ± 31	101 ± 23	115 ± 28	106 ± 25	0.817
HDL-cholesterol (mg/dL)	61 ± 14	68 ± 16	60 ± 21	70 ± 18	0.084
LDL-cholesterol (mg/dL)	105 ± 31	101 ± 23	115 ± 28	106 ± 25	0.300
Triglycerides (mg/dL)	65 (51–79)	63 (50–78)	71 (58–98)	71 (53–85)	0.571
Non-HDL cholesterol (mg/dL)	122 ± 33	117 ± 32	129 ± 33	121 ± 27	0.550
Pharmacological treatment					
Statins (%)	0 (0)	10 (35.7)[a,b]	4 (15.4)	11 (42.3)[a,b]	**0.001**
ACEi/ARB (%)	0 (0)	4 (14.3)[a]	3 (11.5)	9 (34.6)[a]	**0.007**
Antiplatelet drugs (%)	0 (0)	2 (7.1)	1 (3.8)	1 (3.8)	0.619
Statin score	0.0 ± 0.0	87.0 ± 213.8	34.8 ± 107.7	89.4 ± 200.8	0.138
Carotid ultrasound					
Plaque presence	2 (8.3)	6 (21.4)	7 (26.9)	8 (30.8)	0.247
≥ 2 plaques	0 (0)	4 (14.3)	2 (7.7)	3 (11.5)	0.296
≥ 3 plaques	0 (0)	1 (3.6)	1 (3.8)	0 (0)	0.595

Data are shown as n (percentage), mean ± standard deviation or median (Q1-Q3)

[a] P < 0.05 vs T1D–/PE–

[b] P < 0.05 vs T1D–/PE +

[c] P < 0.05 vs T1D + /PE–

* Defined as < 65 years

ACEi Angiotensin-converting enzyme inhibitor, *ARB* Angiotensin receptor blocker, *BMI* Body Mass Index, *CVD* Cardiovascular disease, *DBP* Diastolic blood pressure, *eGFR* Estimated glomerular filtration rate, *HDL* High-density lipoprotein, *LDL* Low-density lipoprotein, *SBP* Systolic blood pressure, *ST1RE* Steno T1 Risk Engine, *T1D* Type 1 diabetes

(15.7 ± 5.7 vs 9.5 ± 5.8; p = 0.001) were also associated with progression.

When analyzed by study groups, significant differences in atherosclerosis progression were observed. Atherosclerosis progression increased in a stepwise manner across the groups, with the lowest prevalence observed in the control group (16.7%, n = 4), higher rates in those with preeclampsia (T1D–/PE + ; 42.3%, n = 11) than T1D (T1D + /PE–; 25.0%, n = 7), and the highest prevalence in those with both conditions (T1D + /PE + ; 57.7%, n = 15) (p

Table 2 Baseline characteristics of the study participants according to the presence of atherosclerosis progression

	All participants (n = 104)	Atherosclerosis progression (n = 37)	No atherosclerosis progression (n = 67)	p-value
General clinical characteristics				
Age (years)	45.2 ± 7.6	48.1 ± 7.8	43.6 ± 7.0	**0.003**
Premature CVD in first-degree relatives* (%)	14 (13.5)	4 (10.8)	10 (14.9)	0.395
Active smoking (%)	21 (20.2)	11 (29.7)	10 (14.9)	0.063
Dyslipidemia (%)	25 (24.0)	12 (32.4)	13 (19.4)	0.107
Hypertension (%)	16 (15.4)	10 (27.0)	6 (9.0)	**0.017**
SBP (mmHg)	121 ± 15	126 ± 16	119 ± 13	**0.015**
DBP (mmHg)	77 ± 9	78 ± 10	77 ± 9	0.603
BMI (kg/m^2)	25.7 ± 5.0	27.0 ± 5.9	25.0 ± 4.3	**0.049**
Waist circumference (cm)	86.4 ± 11.9	87.5 ± 12.2	85.8 ± 11.8	0.507
Obstetrics and gynecology-related characteristics				
No. of pregnancies	2 (1–3)	2 (1–3)	2 (1–3)	0.776
Preeclampsia (%)	52 (50.0)	26 (70.3)	26 (38.8)	**0.002**
Menopause	23 (22.1)	14 (37.8)	9 (13.4)	**0.004**
Diabetes-related clinical characteristics				
T1D (%)	54 (51.9)	22 (59.5)	32 (47.8)	0.174
T1D duration (years) (n = 54)	27.5 ± 7.4	31.2 ± 7.3	24.9 ± 6.4	**0.002**
Diabetic kidney disease (%) (n = 54)	5 (9.3)	2 (9.1)	3 (9.4)	0.676
Diabetic retinopathy (%) (n = 54)	20 (37.0)	11 (50.0)	9 (28.1)	0.089
ST1RE (n = 54)	12.3 ± 6.5	15.7 ± 5.7	9.5 ± 5.8	**0.001**
Laboratory characteristics				
Fasting plasma glucose (mg/dL)	94 (84–148)	95 (85–153)	94 (83–148)	0.804
HbA1c (%)	6.5 (5.2–7.8)	7.2 (5.5–8.0)	6.1 (5.1–7.8)	0.050
Individuals with T1D	7.6 (7.1–8.4)	7.6 (7.2–8.9)	7.7 (7.0–8.4)	0.672
Individuals without T1D	5.1 (5.0–5.4)	5.2 (5.1–5.6)	5.1 (4.9–5.4)	0.151
Serum creatinine (mg/dL)	0.72 ± 0.17	0.69 ± 0.10	0.73 ± 0.20	0.265
eGFR(CKD-EPI; ml/min/1.73m^2)	105 ± 9	103 ± 7	105 ± 10	0.325
Albumin-to-creatinine ratio (mg/g)	4.6 (3.0–10.3)	4.4 (2.3–11.5)	4.8 (3.0–9.2)	0.774
Leucocyte count (10^9/L)	6.5 (4.9–7.7)	6.4 (4.8–8.7)	6.5 (5.0–7.4)	0.807
Total cholesterol (mg/dL)	187 ± 33	190 ± 30	186 ± 34	0.505
HDL-cholesterol (mg/dL)	65 ± 18	63 ± 16	66 ± 18	0.445
LDL-cholesterol (mg/dL)	107 ± 27	113 ± 24	103 ± 28	0.068
Triglycerides (mg/dL)	67 (51–83)	66 (51–77)	69 (52–87)	0.347
Non-HDL cholesterol (mg/dL)	122 ± 31	127 ± 27	120 ± 33	0.258
Pharmacological treatment				
Statins (%)	25 (24.0)	12 (32.4)	13 (19.4)	0.107
ACEi/ARB (%)	16 (15.4)	10 (27.0)	6 (9.0)	**0.017**
Antiplatelet drugs (%)	4 (3.8)	4 (10.8)	0 (0)	**0.014**
Statin score	55 ± 161	70 ± 163	46 ± 161	0.464
Carotid ultrasound				
Plaque presence	23 (22.1)	14 (37.8)	9 (13.4)	**0.005**
≥ 2 plaques	9 (8.7)	4 (10.8)	5 (7.5)	0.404
≥ 3 plaques	2 (1.9)	1 (1.5)	1 (2.7)	0.587

Data are shown as n (percentage), mean ± standard deviation or median (Q1–Q3)

p values for comparisons according to progression status are reported. Bold indicates p < 0.05

*Defined as < 65 years

ACEi Angiotensin-converting enzyme inhibitor, *ARB* Angiotensin receptor blocker, *BMI* Body Mass Index, *CVD* Cardiovascular disease, *DBP* Diastolic blood pressure; *eGFR* estimated glomerular filtration rate, *HDL* High-density lipoprotein, *LDL* Low-density lipoprotein, *SBP* Systolic blood pressure, *ST1RE* Steno T1 Risk Engine, *T1D* Type 1 diabetes

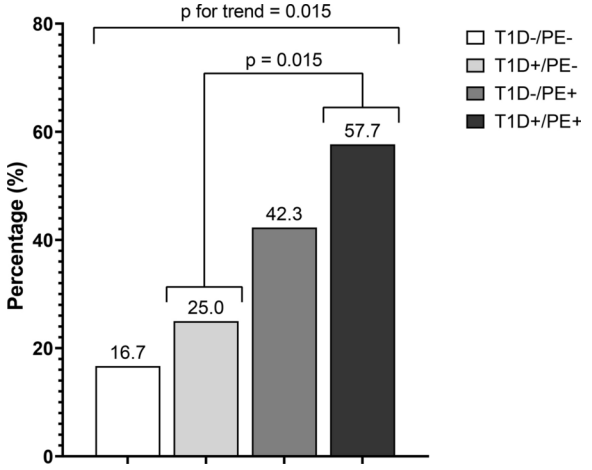


Fig. 1 Presence of atherosclerosis progression (defined as an increase in the number of carotid plaques or incident cardiovascular event) according to the study group. P values for linear trend are reported, as well as P values comparing the T1D and PE group (T1D + /PE +) vs. the T1D-only group (T1D + /PE–). *PE* Preeclampsia, *T1D* Type 1 diabetes

for trend 0.015; p vs T1D + /PE– 0.015; Fig. 1). In logistic regression models, the group with T1D and preeclampsia (T1D + /PE +) was independently associated with atherosclerosis progression in both crude and adjusted models [adjusted OR 7.69 (1.25–47.29), p = 0.028] (Fig. 2, Supplementary Table 2).

Multivariate regression models further assessed the independent contributions of preeclampsia and T1D to atherosclerosis progression (Supplementary Table 2). Even after adjusting for potential confounders such as T1D, CVD risk factors, center, and follow-up time between assessments, preeclampsia was the only factor independently associated with atherosclerosis progression [adjusted OR 4.97 (1.61–15.29), p = 0.005] (Fig. 2, Supplementary Table 2). In an exploratory analysis restricted to participants with T1D, additional adjustment for HbA1c did not attenuate this association, with preeclampsia maintaining strong independent significance [OR 10.10 (1.33–76.87), p = 0.026]. Finally, sensitivity analyses excluding participants with incident CVE (n = 3), baseline DKD (n = 5), or statin use at enrollment (n = 25) consistently demonstrated the persistent association between preeclampsia and atherosclerosis progression (all adjusted p < 0.05), confirming the robustness of our primary findings (Supplementary Table 3).

Discussion

In the present study, preeclampsia emerged as a strong predictor of atherosclerosis progression over a 5-year follow-up period, even after adjusting for major CVRF. Among women already at high cardiovascular risk due to T1D, a synergistic effect was observed. Although no differences were found in estimated 10-year CVD risk, women with both T1D and a

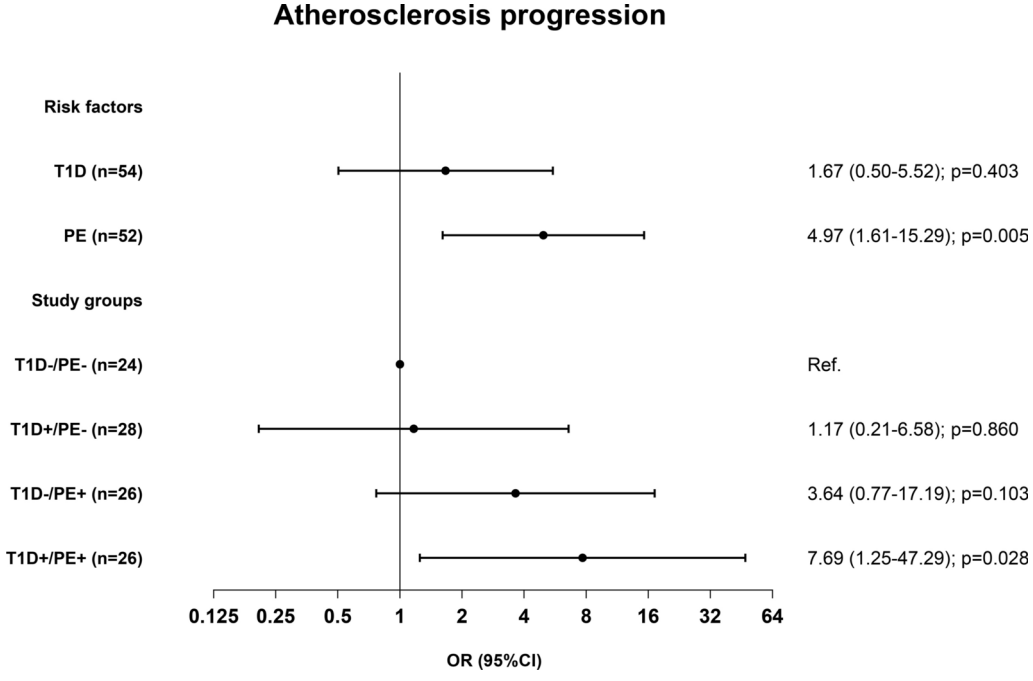


Fig. 2 Logistic regression models for atherosclerosis progression (defined as the occurrence of a cardiovascular event or an increase in the number of carotid plaques) according to T1D and preeclampsia. Fully adjusted logistic regression models (odds ratio and 95% confidence interval) are presented. The first model assessed the presence of T1D or preeclampsia as individual risk factors, while a second model analyzed the study groups. Both models included the following covariates: time since initial visit, center, cardiovascular risk factors (age, systolic blood pressure, LDL-cholesterol, smoking status, body mass index, menopause, and creatinine levels), and statin exposure. *PE* Preeclampsia, *T1D* Type 1 diabetes.

history of preeclampsia experienced twice the rate of atherosclerosis progression compared to those with T1D alone. To our knowledge, this is the first prospective study to independently associate a history of preeclampsia with atherosclerosis progression in women with T1D.

Despite an overall reduction in CVD mortality, the rates of coronary heart disease and CVD mortality continue to rise among young women [27], raising global concern [28]. Several sex-specific factors with a detrimental impact on cardiovascular health have been identified, with preeclampsia emerging as one of the most significant [9, 29]. Although the exact pathophysiology underlying the association between preeclampsia and increased CVD risk has not been fully elucidated, several mechanisms have been proposed. The oxidative stress and inflammatory response resulting from luminal narrowing of the spiral arteries, which transiently supply blood to the endometrium, may persist beyond gestation and contribute to long-term vascular dysfunction and dysregulated lipid metabolism [27]. In this context, we previously reported associations between various inflammatory markers, lipoproteins, and metabolites with atherosclerosis in this high-risk population [30–32]. In the present study, we further observed how women with a history of preeclampsia more frequently experienced atherosclerosis progression, with an independent effect that surpassed and synergized with the already high CVD risk associated with T1D.

The effect of traditional CVRF, such as diabetes, also appears to have a sex-based differential impact, with an excess risk observed in women [28]. Compared to the general population, women with T1D onset before the age of 10 face an almost 60-fold increased risk of ischemic heart disease, compared to a 17-fold increase in men [5]. Hyperglycemia may alter the concentration and activity of estrogen receptors, potentially inhibiting their protective effects on the vascular wall in women [28], although the precise mechanisms remain unclear. Interestingly, a recent multicenter cross-sectional study involving 2,041 patients with T1D observed that women < 55 years with T1D exhibit a similar CVD burden as men, despite having a lower 10-year estimated CVD risk according to ST1RE [33]. Thus, additional risk-enhancing factors should also be evaluated in young women with T1D, whose CVD risk appears to be partially independent of traditional factors and among whom the protective effects of premenopause seem diminished. In this context, the role of preeclampsia, which is more prevalent in women with T1D (10–17% vs 3–5%) [13, 34], warrants further investigation.

The potential contribution of preeclampsia in the development and progression of vascular diabetic complications has been scarcely studied, with most research focusing on microvascular complications [35, 36]. Regarding macrovascular disease, our group has previously shown a higher prevalence of carotid atherosclerosis burden when a history of preeclampsia was present among the T1D population. Moreover, we also reported that this pregnancy-related disorder could partially explain sex-based discrepancies in CVD in individuals with T1D [37]. In a recent Swedish national register-based cohort study, a history of hypertensive disorders of pregnancy was associated with an increased risk of incident CVD in women with T1D; however, this relationship lost significance in fully adjusted models [19]. The analysis of hard events in a young cohort (median age 34.8 years) with a limited follow-up duration (13.0 years), along with the inclusion of varying degrees of hypertensive disorders of pregnancy, may explain the lack of significant results. In the present study, which includes preclinical yet robust markers of future CVE, we observed a two-fold increase in atherosclerosis progression in women with T1D and a history of preeclampsia, despite no differences in 10-year CVD risk estimation between groups with or without this pregnancy-related disorder. Moreover, a strong and independent effect of preeclampsia was confirmed in fully adjusted multivariate regression models.

Our study has some limitations. First, the association was based on an observational study and thus, causality cannot be established. Additionally, the relatively short follow-up period may be insufficient to capture atherosclerosis progression in a young cohort, which could explain the low number of events observed. Furthermore, despite being an independent predictor of CVE [38], the assessment of carotid plaques by ultrasound is a surrogate variable and hard clinical events should be assessed in further long-term prospective studies. While we adjusted for statin exposure using a lifetime dose metric, our study could not evaluate potential effects of other cardioprotective medications introduced during follow-up, which may also influence atherosclerosis progression. Finally, the inclusion of a single sample of patients from two tertiary centers, all belonging to the same ethnicity, may limit the representativeness of the findings and restrict their generalizability to other regions, healthcare settings, or more diverse populations. Future research should prioritize inclusion of other ethnic groups, particularly those with elevated preeclampsia susceptibility, to strengthen external validity.

This study also has several strengths. To our knowledge, it is the first study to demonstrate a significant association between preeclampsia and atherosclerosis progression in individuals with T1D. Furthermore, the careful selection of participants, matching for several CVRF among groups, and thorough review of medical records regarding gestational information reduced the risk of bias. Finally, the robustness of our results lies in the prospective design of the study and the inclusion

of major confounders in multivariate analyses, which reduces potential confounding biases and enhances the reliability of the observed associations.

In conclusion, this prospective study demonstrates that a history of preeclampsia is significantly associated with carotid plaque progression and CVE, even after adjusting for major CVRF. Moreover, an additive effect was observed in women already at high cardiovascular risk due to T1D. Specifically, in women with T1D, a history of preeclampsia was associated with a twofold increase in the risk of atherosclerosis progression, despite no significant differences in predicted CVD risk. These findings support incorporating preeclampsia as a risk-enhancing factor in CVD prevention guidelines for T1D, with parallel evaluation for its integration into existing specific risk prediction calculators. This is particularly relevant for younger women with T1D, whose CVD risk may not be fully captured by traditional factors and for whom the protective CVD effects of premenopause appear to be diminished.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02719-3.

Supplementary Material 1.

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Author contributions
All authors have discussed the results and commented on the final version of the manuscript. A.P., I.V., E. L.-Q., E. M., N. A., C.Q. A.J.A. and V.P. acquired and processed all clinical data; A.J.A. and V.P performed the US measurements. A.J.A. and V.P. contributed to the study concept and design. A.M, C.P.-J., V.P. and A.J.A. participated in data analysis and interpretation. A.M., V.P. and A.J.A. wrote the manuscript, designed the figures, and had final responsibility for the decision to submit for publication. A.J.A. and V.P. are the guarantors of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Availability of data and materials
No datasets were generated or analyzed during the current study.

Declarations

Ethics approval and consent to participate
The study was approved by the Ethics Committees in Barcelona (HCB/2021/1070) and Terrassa (P21-111). Informed consent was obtained from all participants before study-specific procedures.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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