ORIGINAL ARTICLE

Association between endometriosis and increased arterial stiffness

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KEY WORDS
arterial stiffness, atherosclerosis, endometriosis

ABSTRACT

BACKGROUND Endometriosis is a common gynecologic disease associated with systemic inflammation and atherogenic risk factors. Therefore, women with endometriosis may have increased cardiovascular risk.

AIMS We aimed to evaluate arterial stiffness using cardio–ankle vascular index (CAVI) in women with and without endometriosis.

METHODS We enrolled 44 patients with endometriosis and 76 age-matched controls without endometriosis. Endometriosis was diagnosed based on histopathologic examination or magnetic resonance imaging. Arterial stiffness was evaluated using CAVI in all study participants.

RESULTS No differences were observed between patients and controls in terms of age (median [interquartile range, IQR], 30 [24.25–5] years and 26 years [24–35] years, respectively), body mass index (median [IQR], 23.31 [20.82–24.98] kg/m^2 and 23.74 [21.13–26.78] kg/m^2, respectively), or waist circumference (median [IQR], 69 [64–75] cm and 72 [65–81.25] cm, respectively). C-reactive protein levels were higher in women with endometriosis than in controls (median [IQR], 0.27 [0.14–0.68] mg/dl vs 0.12 [0.06–0.24] mg/dl; P <0.001). Left ventricular ejection fraction, left ventricular mass index (LVMI), relative wall thickness, as well as systolic and diastolic blood pressures were similar in both groups. Women with endometriosis had higher CAVI than controls (mean [SD], 5.961 [0.644] vs 5.554 [0.654]; P = 0.001). Elevated arterial stiffness was observed in the endometriosis group also after adjustment for age and LVMI.

CONCLUSIONS Our results indicate increased arterial stiffness measured by CAVI in women with endometriosis. Therefore, clinicians should be aware that these patients may be at increased cardiovascular risk.

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INTRODUCTION Endometriosis is a common gynecologic disorder characterized by the presence of endometrium-like tissue at sites outside the uterine cavity.[1] Although immunologic and inflammatory factors are known to play an important role, the pathophysiology of this complex condition is yet to be fully understood. In general, it was reported that a local sterile inflammation occurs in the peritoneal cavity of women with endometriosis.[2] However, studies on endometriosis indicated also elevated inflammatory[3,4] and oxidative stress[5] markers in peripheral blood. This suggests that the disease is also associated with chronic systemic inflammation. It is well recognized that chronic inflammatory processes play a central role in the initiation and progression of atherosclerosis.[6] Moreover, women with endometriosis have a higher risk of hypercholesterolemia and hypertension, which are well-known risk factors for atherosclerotic cardiovascular disease (CVD).[7,8] In addition, endometriosis and CVD may share a common genetic background.[9] Overall, the proinflammatory milieu, accompanied by atherogenic risk factors

WHAT'S NEW?

Endometriosis is a common disorder associated with systemic inflammation and atherogenic risk factors. The cardio–ankle vascular index (CAVI) has been established as an index of arterial stiffness. This study found higher CAVI values in young women with endometriosis, suggesting increased arterial stiffness without a significant alteration in echocardiographic parameters. To our knowledge, this is the first study showing increased arterial stiffness, as measured with CAVI, in women with endometriosis, indicating subclinical cardiovascular disease. Clinicians should be aware of the possible increased cardiovascular risk in women with endometriosis.

and possible genetic predisposition, can lead to increased cardiovascular risk in patients with endometriosis. The prospective NHS II study (Nurses' Health Study II) reported that women with endometriosis had a higher risk of myocardial infarction, angiographically confirmed angina, and coronary revascularization, independent of possible confounding variables when compared with women without endometriosis.[9] However, as endometriosis is typically diagnosed at a relatively young age, risk estimation and diagnosis of CVD is possible when it is still in the subclinical stage.[10]

Arterial stiffness is one of the earliest manifestations of structural and functional alterations within the vessel wall.[11] Increased arterial stiffness has been associated with cardiovascular risk factors, subclinical target organ damage, presence of atherosclerotic CVD, as well as the risk of future fatal and nonfatal cardiovascular events.[12-14] Several noninvasive methods have been developed over the years to estimate arterial stiffness, and they are increasingly being used to evaluate cardiovascular risk. Recently, the cardio–ankle vascular index (CAVI) has been established as an index of arterial stiffness. One of the advantages of using CAVI is that it is predominantly operator independent and has high reproducibility. Moreover, it is relatively independent from blood pressure (BP) measurements.[15]

This study aimed at comparing early changes in the arterial wall by measuring CAVI in women with and without endometriosis. Additionally, we assessed the metabolic profile and echocardiographic parameters in both groups.

METHODS **Study population** Female patients aged between 20 and 50 years and admitted to a university outpatient clinic between May 2019 and January 2020 were enrolled in this single-center observational study. The control group included age-matched healthy women who attended the gynecology clinic for contraception or other gynecologic issues. Matching was achieved by recruiting 2 participants who were within 5 years of age of one another. Women without left ventricular (LV) systolic dysfunction, valvular heart disease, atrial fibrillation, or established peripheral artery disease were invited to participate in the study. The inclusion criteria for the control group included documentation of normal ovarian morphology on ultrasonography without any finding of endometriosis. The exclusion criteria for all participants were as follows: current pregnancy or breastfeeding, presence of any chronic disease (eg, diabetes mellitus, autoimmune disorder, kidney disease, and liver disease), smoking, use of hormonal contraceptives (current or within up to 6 months before the study), history of arterial or venous thrombosis; left ventricular ejection fraction (LVEF) of less than 50%, moderate to severe valvular disease on echocardiography, a history of peripheral artery disease (established by angiography, Doppler arterial examination). Women with a history of oophorectomy or hysterectomy were also excluded from the study. With a planned case-to-control ratio of 1:2, a total of 44 endometriosis cases and 88 controls were recruited. Twelve patients in the control group were excluded from the final analysis because they did not participate in the CAVI measurements or subsequent gynecologic examinations. The diagnosis of endometriosis was reached on the basis of biopsies or magnetic resonance imaging.

The study was approved by the local ethics committee and was conducted according to the Declaration of Helsinki. Informed consent was obtained from all participants before inclusion in the study.

Clinical data collection Demographic characteristics, medical history, medication use, and anthropometric measurements were recorded during patient interviews. The body mass index (BMI) was determined as body weight (kg) / height (meters) squared. A BMI of less than 25 kg/m^2 was defined as normal, and a BMI between 25 and 30 kg/m^2 indicated overweight. Routine laboratory test results were obtained from the hospital records. All subjects underwent transvaginal or transabdominal ultrasonography with Voluson 730 Pro (GE Healthcare, Istanbul, Turkey). Blood levels of fasting plasma glucose, insulin, total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), C-reactive protein (CRP), cancer antigen 125 (CA-125), and anti-Müllerian hormones were determined. Insulin resistance was estimated using the homeostatic model assessment (HOMA-IR: fasting serum insulin [μIU/ml] × fasting plasma glucose [mmol/l]/22.5). In most cases, endometriosis was diagnosed on the basis of histopathologic examination. In the remaining cases, the diagnosis was established based on typical endometrioma findings on magnetic resonance imaging.

Echocardiographic evaluation All women with endometriosis and a subgroup of age-matched controls underwent a comprehensive echocardiographic examination performed by

a single physician (C.I.S), using an available echocardiography device (Vivid 7, GE Vingmed Ultrasound, Horten, Norway). The images were obtained from the left parasternal long-axis, short-axis, and apical 4-chamber views. Left ventricular ejection fraction, LV mass index (LVMI), and relative wall thickness (RWT) were calculated from LV dimensions obtained by M-mode echocardiography. Left ventricular mass was estimated using the following formula[16]: $0.8 \times \{1.04 \times [(LVIDd + PW + IVSd)^3 \times (LVIDd)^3]\} + 0.6$ g, where LVIDd denotes end-diastolic left ventricular internal dimension; PW, posterior wall thickness; and IVSd, interventricular septal diameter.

Left atrial volume was estimated using the biplane area-length formula:

$$V = \frac{8}{3\pi}\left[\frac{(A1)\times(A2)}{L}\right],$$

where A1 and A2 represent the left atrial area in the apical 4-chamber and apical 2-chamber views, respectively, while L represents the long-axis length measured in the apical 4-chamber window at ventricular end-systole (maximum left atrial size).[17] The LVMI was calculated by indexing the LV mass to the body surface area. Tissue doppler recordings (e' and a') were obtained from LV septal and lateral walls. To assess diastolic function, transmitral E velocity obtained by pulsed Doppler was divided by the average of septal and lateral e'.

Cardio–ankle vascular index Arterial stiffness was assessed using CAVI by the same physician (C.I.S) in patients with endometriosis and controls. The index was measured using VaSera TM (VS-1500 system, Fukuda Denshi, Tokyo, Japan), as described previously.[18] The cuffs were placed around each of the 4 extremities, while

TABLE 1 Clinical features and laboratory variables of the study group

Parameter	Controls (n = 44)	Women with endometriosis (n = 76)	*P* value
Age, y	26 (24–35)	30 (24.25–35)	0.46[a]
BMI, kg/m^2	23.74 (21.13–26.78)	23.31 (20.82–24.98)	0.13[a]
Waist circumference, cm	72 (65–81.25)	69 (64–75)	0.18[a]
Systolic BP, mm Hg	120.62 (12.40)	120.05 (9.34)	0.77
Diastolic BP, mm Hg	71.02 (8.77)	69.68 (7.94)	0.41
CRP, mg/dl	0.12 (0.06–0.24)	0.27 (0.14–0.68)	<0.001[a]
TC, mg/dl	179.06 (36.41)	166.47 (32.05)	0.1
LDL-C, mg/dl	103.63 (31.80)	91.16 (23.84)	0.05
HDL-C, mg/dl	53.68 (16.59)	59.44 (12.51)	0.08
Triglycerides, mg/dl	91 (66–122)	67 (57–84.75)	0.007[a]
Fasting glucose, mg/dl	90.41 (5.83)	90.47 (7.95)	0.79
Fasting insulin, mU/l	8.43 (6.11–10.65)	8.19 (6.78–9.64)	0.81[a]
HOMA-IR	1.85 (1.36–2.38)	1.89 (1.44–2.28)	0.81[a]
Anti-Müllerian hormones, µg/l	5.42 (3.6–7.8)	2.41 (0.99–4.39)	<0.001[a]
CAVI	5.55 (0.654)	5.96 (0.644)	0.001
LVEF	61.86 (4.84)	62.08 (5.72)	0.85
LVMI, g/m^2	65.49 (16.08)	71.71 (13.58)	0.05
RWT	0.39 (0.37–0.43)	0.40 (0.37–0.42)	0.66[a]
E/e'	6.36 (1.22)	5.89 (1.35)	0.09

Normally distributed continuous parameters were presented as mean (SD) and skewed variables were presented as median (interquartile range).

SI conversion factors: to convert TC, LDL-C, and HDL-C to mmol/l, multiply by 0.0259; triglycerides to mmol/l, by 0.0113; glucose to mmol/l, by 0.0555; C-reactive protein to nmol/l, by 9.524.

a *P* values were calculated with the Mann–Whitney test.

Abbreviations: BMI, body mass index; BP, blood pressure; CAVI, cardio–ankle vascular index; CRP, C-reactive protein; E/e', the ratio of the transmitral early peak velocity over early diastolic mitral annulus velocity; LVEF, left ventricular ejection fraction; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; LVMI, left ventricular mass index; RWT, relative wall thickness; TC, total cholesterol

TABLE 2 Associations between cardio–ankle vascular index and clinical or laboratory parameters

Parameters	Unstandardized β coefficient	95% CI for unstandardized β coefficient	*P* value
All participants			
Age, y	0.039	0.021–0.057	<0.001
BMI, kg/m^2	0.020	−0.055 to 0.094	0.61
Waist circumference, cm	−0.019	−0.047 to 0.010	0.2
HOMA-IR	−0.061	−0.198 to 0.076	0.38
Systolic BP, mm Hg	−0.010	−0.024 to 0.004	0.17
Diastolic BP, mm Hg	0.017	−0.001 to 0.034	0.06
Endometriosis group			
Age, y	0.053	0.019–0.086	0.003
BMI, kg/m^2	0.056	−0.063 to 0.175	0.35
Waist circumference, cm	−0.040	−0.085 to 0.004	0.08
HOMA-IR	0.071	−0.243 to 0.385	0.65
Systolic BP, mm Hg	−0.011	−0.036 to 0.014	0.36
Diastolic BP, mm Hg	0.009	−0.020 to 0.037	0.55

Abbreviations: see TABLE 1

the electrocardiogram electrodes were placed on both wrists. In order to record the aortic valve sound, the phonocardiograph was fixed at the second rib line of the sternum. Then, brachial BP and pressure waveforms of the brachial and tibial arteries were recorded noninvasively after at least 10 minutes of bed rest, using pulse volume waveforms obtained at right and left sides. Mean CAVI values were calculated. Patients with low ankle–brachial index (ABI) values (<0.9) were excluded from analysis during the calculation.

Sample size calculation and statistical analysis The sample size was calculated to be at least 42 in the endometriosis group by using G*Power 3.1.[19] This would achieve a power of 90% with an α error of 0.05 for detecting a 0.5 difference in mean CAVI values with a presumed standard deviation of 0.77 and a mean CAVI of 5.5 in the control group (based on previous pilot CAVI results in our department). Data visualization and analysis were performed using the R statistical computing software version 3.5.3 (Vienna, Austria) with the R commander 2.6 package as well as IBM SPSS Statistics for Windows, version 20.0 (IBM, Armonk, New York, United States). Continuous variables were examined using visual inspection and the Shapiro–Wilk test for normality. Normally distributed continuous variables were presented as mean (SD). If the distribution of the variables was skewed, they were presented as median (interquartile range [IQR]). For categorical variables, percentage values were presented together with frequencies. Normally distributed continuous variables were analyzed using the *t* test. For differences in mean, 95% CIs were also calculated. The Mann–Whitney test was used for the nonnormally distributed continuous variables. A bivariate Pearson correlation test was performed to assess correlations between CAVI values and other parameters. A multivariable analysis was performed by constructing a multiple linear regression model to analyze the independent effects of various factors on CAVI. The analysis of covariance was used to determine CAVI values adjusted for age. Statistical significance level was set at a *P* value of less than 0.05.

RESULTS A total of 120 women were included in the final analysis (44 cases with endometriosis and 76 controls). The median (IQR) duration of documented endometriosis was 18 (12–36) months. In the endometriosis group, 35 women (79.5%) had ovarian endometriotic cysts, 7 (15.9%) had peritoneal endometriosis, and 2 (4.5%) had abdominal wall endometriosis. Only 4 women underwent ovarian endometriotic cyst excision and none of the patients had a history of oophorectomy or hysterectomy.

The baseline characteristics of participants are presented in TABLE 1. Median age, BMI, and waist circumference were comparable between endometriosis and control groups. Systolic and diastolic BP were also similar. In contrast, anti-Müllerian hormone and triglyceride levels were significantly lower in the endometriosis group, while CRP levels were increased in women with endometriosis (TABLE 1). In the endometriosis group, CA-125 levels were higher

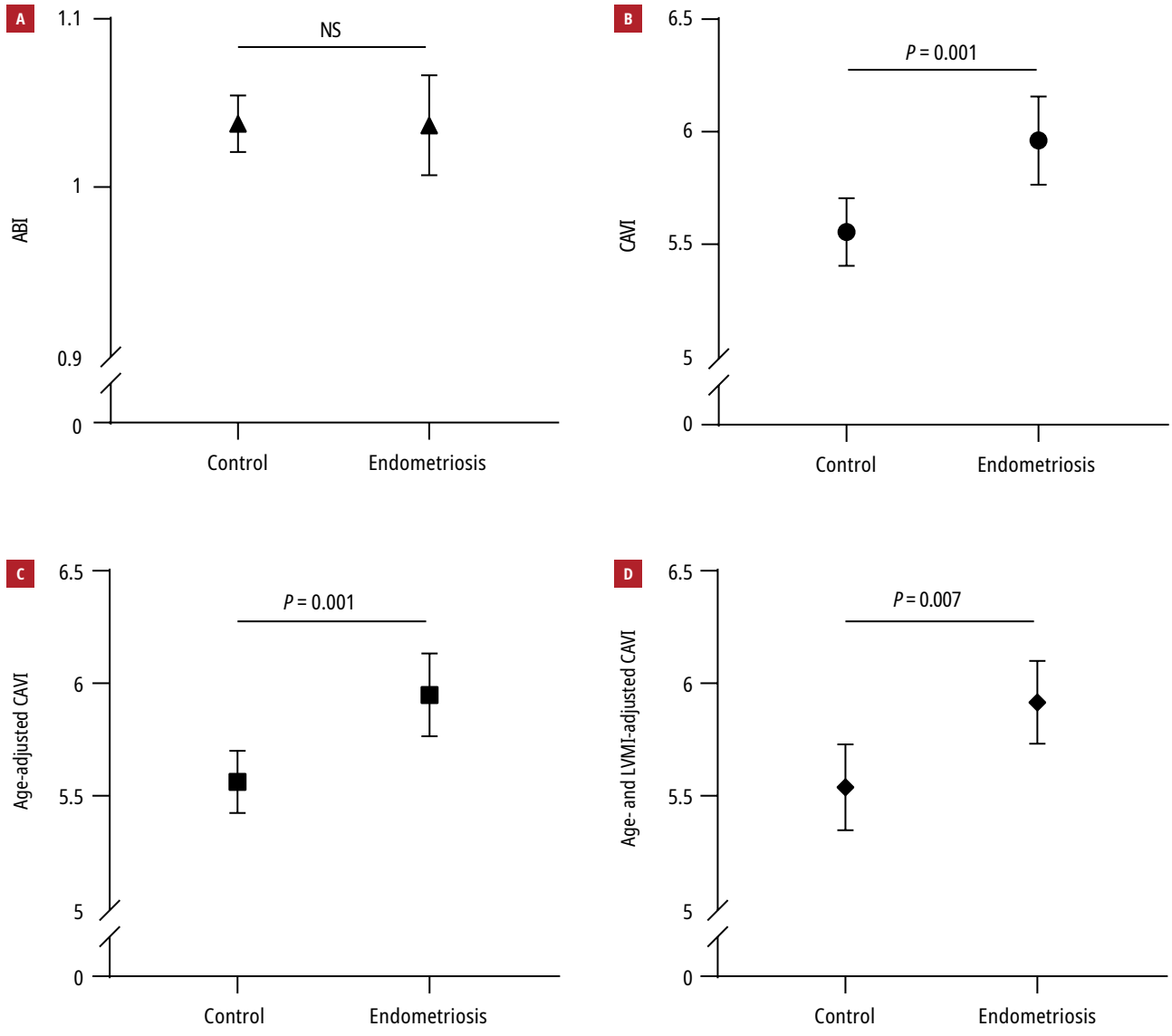

FIGURE 1 Comparison of arterial stiffness parameters between study groups. Data are presented as mean values. Triangles, circles, squares, and diamonds represent mean values. Whiskers represent SD.
Abbreviations: ABI, ankle–brachial index; NS, nonsignificant; others, see TABLE 1

(median [IQR], 41.30 [22.43–92.25] U/ml) than the laboratory cutoff value (35 U/ml), as expected. The mean CAVI value in the endometriosis group was also found to be higher when compared with controls (TABLE 1).

Associations between CAVI and clinical or laboratory parameters were evaluated using a multiple regression analysis (TABLE 2). Overall, in all participants, only age (unstandardized β coefficient = 0.039; P <0.001) was correlated with CAVI. Similarly, age was found to be the only independent predictor of CAVI (unstandardized β coefficient = 0.053; P = 0.003) in the endometriosis group when age, BMI, waist circumference, as well as systolic and diastolic BP were all included in the model.

The CAVI was compared between groups after determining the ABI value. There was no difference in mean ABI between groups (FIGURE 1A). On the other hand, mean CAVI was higher in the endometriosis group when compared with controls (mean difference = 0.407; 95% CI, 0.163–0.651; P = 0.001; FIGURE 1B). Since age was documented to be independently correlated with CAVI, a covariance analysis was performed with adjustment of CAVI for age. The analysis revealed that age-adjusted CAVI was also higher in women with endometriosis (age-adjusted mean difference = 0.386; 95% CI, 0.160–0.613; P = 0.001; FIGURE 1C).

Subsequently, the study groups were compared in terms of echocardiographic parameters describing cardiac chamber function and wall thickness. No differences in LVEF, LV wall thickness, or diastolic function were observed (P >0.05). Bivariate correlations between CAVI and LVMI, LVEF, RWT, and E/e' were also assessed. Only LVMI was found to be a significant

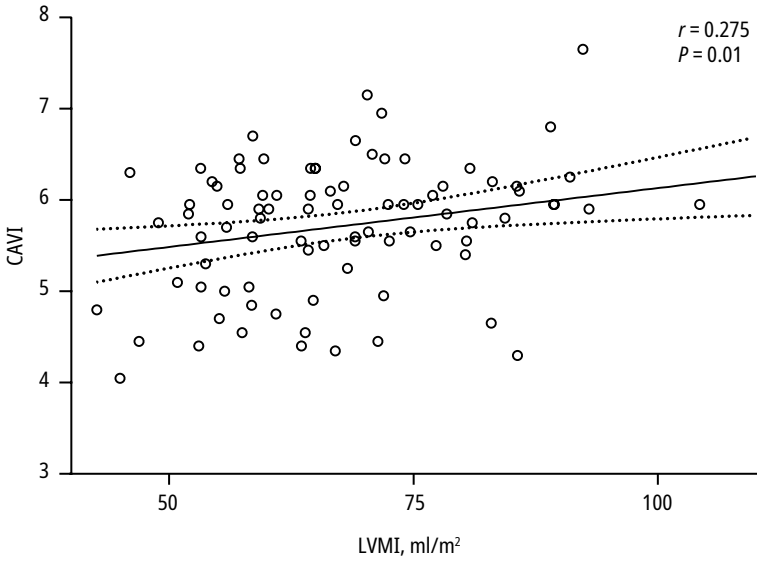

FIGURE 2 Correlations between left ventricular mass index (LVMI) and cardio–ankle vascular index (CAVI)

independent predictor of CAVI (FIGURE 2). Therefore, CAVI was further adjusted for LVMI together with age. The results showed that CAVI was higher in women with endometriosis compared with controls even after controlling for the effects of age and LVMI (FIGURE 1D). Next, we built another model including triglyceride levels in addition to age and LVMI. This model also revealed a higher CAVI in the endometriosis group (mean difference = 0.334; 95% CI, 0.027–0.641; $P = 0.03$).

DISCUSSION The objective of the current study was to compare arterial stiffness measured by CAVI between women with endometriosis and BMI- and age-matched controls. Moreover, we aimed to evaluate potential associations between CAVI and any clinical or laboratory parameters. Our main finding was that arterial stiffness measured by CAVI was higher in women with endometriosis as compared with controls. Adjusted CAVI values were also found to be higher in the endometriosis group, while the groups did not differ in terms of LVEF, LVMI, or RWT.

Endometriosis has been associated with chronic inflammation, increased oxidative stress, and atherogenic risk factors, all of which may lead to a higher risk of atherosclerotic CVD. The NHS II study, which included 116 430 registered female nurses, reported a higher risk of myocardial infarction (relative risk [RR], 1.52; 95% CI, 1.17–1.98), angiographically confirmed angina (RR, 1.91; 95% CI, 1.59–2.29), and coronary revascularization procedures (RR, 1.35; 95% CI, 1.08–1.69) in women with confirmed endometriosis, independent of potential confounders.[9] Of note, the highest RR for the combined endpoints was noted in women younger than 40 years and decreased as age increased.[9] However, atherosclerotic CVD is a complex disease that begins at an early age and develops over decades. Endometriosis is also diagnosed at a young age, which may provide a window-of-opportunity for the detection of subclinical atherosclerosis and better risk stratification in these women.[10] Noninvasive measurements of subclinical atherosclerosis evaluating different aspects of the atherosclerotic process are widely used.[20] Endothelial dysfunction is one of the earliest recognizable signs of atherosclerosis and precedes structural changes in the arterial wall. Therefore, it can be used as a marker of atherosclerotic risk.[21] Kinugasa et al[22] found significantly lower flow-mediated dilation (FMD) in the brachial arteries of women with endometriosis than in those without, indicating endothelial dysfunction. Similarly, Santoro et al[23] found lower levels of FMD in endometriosis. Moreover, in a follow-up study, the authors showed significantly improved FMD in patients who underwent surgical treatment, reaching comparable levels to those in controls.[24]

Arterial stiffness is another marker of early changes in the arterial wall. In their study, Pretta et al[25] measured the intima–media thickness and distensibility coefficient in the common carotid artery in women with endometriosis and found no significant difference in these parameters as compared with controls. Santoro et al[23] also failed to show a difference in carotid intima–media thickness despite increased levels of several inflammatory markers and decreased FMD. In a recent study, there was no difference between women with endometriosis and controls in the mean CAVI when adjusted for age and ABI.[26] On the contrary, Tani et al[20] measured brachial–ankle pulse wave velocity to determine arterial stiffness in 28 Japanese women with endometriosis and 21 controls. In line with our current findings, they found that women with endometriosis aged over 30 years had significantly higher arterial stiffness than those without endometriosis. On the other hand, when women were categorized according to age, pulse wave velocity was similar in women with and without endometriosis under the age of 30 years.[20] However, it is important to note that a small sample size in this group could affect the generalizability of these results (6 patients and 6 controls). Possible explanations for the discrepancy between these studies include the heterogeneity of the disease, differences in age and race, sensitivity of the applied technique, and the small sample size.

Dyslipidemia is a well-established risk factor for atherosclerotic CVD. Endometriosis can lead to an unfavorable lipid profile through various mechanisms, such as systemic inflammation, medication use, and treatment with hysterectomy or oophorectomy.[8,27] A number of studies compared blood lipid levels of women with endometriosis to

those in controls and reported conflicting results. Verit et al[28] and Melo et al[7] found higher total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels, whereas other studies reported similar levels.[20,22,23] Results regarding HDL-C levels are also inconsistent. While some studies reported similar[22] or even increased HDL-C levels compared with controls,[7,23,29] others found decreased levels.[5,20,28] Nevertheless, significant differences between the groups in these studies do not necessarily indicate an atherogenic lipid profile. For instance, in a study by Tani et al,[20] women with endometriosis had lower mean HDL-C levels than controls. However, these levels were still the desirable levels (60.1 [10] vs 72.5 [12.4]; P <0.01).[20] In the current study, lipid levels were similar between groups, except for lower triglyceride levels in women with endometriosis. Another important atherogenic molecule is a low-density-lipoprotein–like particle, lipoprotein(a). Crook et al[29] reported higher lipoprotein(a) levels in the endometriosis group than in controls (15 vs 3.1 mg/dl; P <0.05). Mu et al,[8] investigated both directions of associations between endometriosis and dyslipidemia in the NHS II research. They found not only that endometriosis was prospectively associated with an increased risk of hypercholesterolemia and hypertension, but also that hypercholesterolemia and hypertension were prospectively associated with a higher risk of laparoscopically confirmed endometriosis.[8]

The arterial system is closely related to the LV. Consequently, previous studies suggested an association between arterial stiffness and LV function (particularly diastolic).[30-32] In the current study, several echocardiographic parameters were compared between women with and without endometriosis. However, the groups did not differ in terms of LVMI and LV diastolic function, despite a significant overall correlation between CAVI and LVMI. Apart from ventricular functions, Kikuya et al[33] proposed ambulatory arterial stiffness index derived from 24-hour ambulatory BP monitoring as a surrogate measure of arterial stiffness. Interestingly, they documented that increased short-term variability in BP is associated with target organ damage. However, data on the relationship of endometriosis with BP variability are lacking, and the long-term consequences of such variability in women with endometriosis need to be addressed in future research. It was reported that although men and women have a similar prevalence of symptomatic heart failure, cardiac maladaptation to arterial stiffening is different in women.[34] This discrepancy may be at least partially explained by diseases specific to women (such as endometriosis), and more studies are urgently needed to assess whether previous endometriosis may contribute to heart failure in women at an older age.

Our study has several limitations. First, we assessed only CRP levels, while the measurement of other systemic inflammatory markers and oxidative stress parameters would facilitate better understanding of the relationship between CAVI and chronic inflammation. This, in turn, might help identify higher-risk patients. Furthermore, the observational design of this study makes it impossible to identify long-term risks in this population of patients. Second, other cardiovascular risk factors, such as family history, were not assessed. Third, the exact duration of the disease could not be determined, while this is as a possible long-term risk factor. Finally, our results cannot be extrapolated to postmenopausal groups because of the relatively young age of the study population.

Conclusions Endometriosis is a common gynecologic disorder associated with systemic inflammation and atherogenic risk factors. We found higher CAVI in women with endometriosis, without significant alterations in echocardiographic parameters. This indicates subclinical CVD in women with endometriosis. It is important to raise awareness among clinicians of the possible increased cardiovascular risk in women with endometriosis.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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