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Endothelial progenitor cells in polycystic ovary syndrome according to insulin resistance status

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Abstract

Aim: Polycystic ovary syndrome (PCOS) is associated with increased cardiovascular disease (CVD) risk, particularly with insulin resistance (IR). Endothelial progenitor cells (EPCs) contribute to vascular repair. This study evaluated circulating EPC number in women with anovulatory PCOS with and without IR, and its relationship with cardiovascular risk markers.

Methods: In this cross-sectional study, 40 newly diagnosed, treatment-naïve women with anovulatory PCOS (2003 Rotterdam criteria) were divided into two groups of 20 according to the presence or absence of IR (HOMA-IR ≥2.7), and compared with 20 age- and sex-matched healthy controls. Circulating EPCs (CD34+/CD133+/VEGFR-2+ cells) were quantified by flow cytometry. Metabolic, hormonal and inflammatory parameters, together with serum VEGF, ICAM-1, VCAM-1, E-selectin and MMP-9, were measured by ELISA.

Results: Glucose, triglyceride, hs-CRP, fibrinogen, ferritin, E-selectin and MMP-9 were significantly higher, and HDL-cholesterol significantly lower, in the IR-positive group compared with controls ($P < .05$). ICAM-1 and VEGF did not differ significantly among groups. In the IR-negative group, VCAM-1 was the only inflammatory or endothelial marker significantly higher than in controls ($P = .010$). Circulating EPC numbers did not differ significantly between either PCOS group and controls, and EPC counts correlated weakly with FSH (Spearman rho=0.258, $P = .046$; exploratory).

Conclusion: In young, newly diagnosed women with PCOS, inflammatory and endothelial-activation markers were increased predominantly in the IR-positive group, which also had a higher BMI, so the effects of IR and adiposity cannot be separated. Circulating EPC numbers did not differ significantly between groups; larger studies with functional EPC assays are needed.

Keywords

polycystic ovary syndrome, insulin resistance, endothelial progenitor cells, heart disease risk factors

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Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age, affecting 10–13% of women in this age group, with lifelong effects extending from adolescence to the postmenopausal period. After exclusion of other etiological causes, the diagnosis is established by the presence of at least two of the following: chronic oligo-anovulation, clinical and/or biochemical hyperandrogenism, and polycystic ovarian morphology.[1,2]

Insulin resistance (IR) and compensatory hyperinsulinemia play a central role in the pathophysiology of PCOS. IR is present in 65–95% of women with PCOS. Although IR can occur in both normal-weight and obese women, it tends to be more pronounced in obese women.[1,3] Women with PCOS have an increased prevalence of cardiovascular risk factors such as dyslipidemia, obesity, impaired glucose tolerance, type 2 diabetes mellitus, and hypertension.[4] Contemporary cardiometabolic reviews emphasize that PCOS should be regarded not merely as a reproductive disorder but as a lifelong metabolic condition requiring cardiovascular risk stratification 1. For this reason, it has recently also been termed polyendocrine metabolic ovary syndrome (PMOS).

Endothelial progenitor cells (EPCs) are bone-marrow-derived cells first described by Asahara et al. in 1997.[5] They are mobilized into the circulation in response to vascular injury and ischemia, and have the capacity to differentiate into mature endothelial cells and contribute to endothelial regeneration and neovascularization.[6] EPC mobilization from the bone marrow is regulated by vascular endothelial growth factor (VEGF), stromal-cell-derived factor-1, and activation of matrix metalloproteinase-9 (MMP-9).[5,6] EPC dysfunction has been linked to cardiovascular risk factors particularly IR, but also hypertension, type 2 diabetes and dyslipidemia as well as to cardiovascular events such as coronary artery disease and stroke.[7,8,9,10]

Studies have shown a relationship between EPCs and insulin resistance. Biochemical abnormalities seen in IR reduced nitric-oxide bioavailability, increased reactive oxygen species, and attenuated PI3-kinase-mediated signaling impair EPC mobilization from the bone marrow, reducing circulating EPC number and impairing endothelial adhesion, integration and proliferation capacity. IR is thus thought to impair EPC-mediated endothelial regeneration, which may contribute to atherosclerosis and cardiovascular risk.[6]

A limited number of studies evaluating EPCs in women with PCOS have reported conflicting results: some studies report reduced EPC number and impaired in-vitro tube formation in PCOS,[11] while another study in non-hyperandrogenic, non-classic PCOS found significantly lower fasting CD133+, CD34+ and CD133+CD34+ cell counts compared with controls, together with blunted CD133+ cell mobilization after a 75-g oral glucose load.[12] Other studies have found no significant difference in EPC number between women with PCOS and controls, independent of obesity.[13,14] In a recent, large case-control study of 84 women with PCOS and 76 controls, although EPC proliferative capacity was not significantly reduced, EPC migration and tube-formation capacity were significantly impaired in PCOS, an effect linked to up-regulation of miRNA-339-5p and consequent suppression of the PI3K/AKT and SIRT1/PGC-1α signaling pathways.[15]

Studies have shown that PCOS is characterized by low-grade chronic inflammation and endothelial dysfunction.[16,17,18] Inflammation plays an important role in the development and progression of atherosclerotic complications and increases the risk of coronary artery disease and type 2 diabetes. Elevated CRP, leukocyte count, cytokines, and adhesion molecules such as ICAM-1, VCAM-1 and E-selectin have been shown to be markers of inflammation in PCOS.[16,17,18,19] Many studies have reported increased MMP-9 levels in women with PCOS, supporting its role as a marker of the low-grade inflammatory state characteristic of the syndrome.[20,21] Serum VEGF findings in PCOS, on the other hand, remain more heterogeneous in the literature.

The aim of this study was to characterize circulating EPC number together with inflammatory and endothelial-activation markers in young, newly diagnosed, treatment-naïve women with PCOS, with and without IR, and to examine their relationship with other cardiovascular risk markers.

Materials and Methods

Study Design

Forty women with newly diagnosed, treatment-naive anovulatory PCOS presenting to the endocrinology outpatient clinic were enrolled. PCOS was diagnosed according to the revised 2003 Rotterdam criteria, requiring at least two of the following three findings after exclusion of other etiological causes: oligo-anovulation, clinical and/or biochemical hyperandrogenism, and polycystic ovarian morphology on ultrasonography 2. Patients were divided into two groups according to the presence or absence of IR. Twenty age- and sex-matched healthy volunteers served as the control group. Age did not differ significantly among the groups ($P = .070$). IR was defined using the homeostasis model assessment of insulin resistance (HOMA-IR), calculated as [fasting insulin (μU/mL) × fasting glucose (mg/dL)]/405.[22] HOMA-IR value ≥2.7 was accepted as indicating IR. Exclusion criteria included diabetes mellitus, hepatic or renal dysfunction, coronary artery disease, hypertension, active smoking, use of oral contraceptives, and use of medications affecting glucose, lipid, blood pressure or platelet function.

Venous blood samples (10 mL) were obtained from all participants between menstrual cycle days 2–5, after an 8–12-hour overnight fast. Cells expressing CD34, CD133 and VEGF receptor-2 were identified as EPCs by flow cytometry in the hematology laboratory. Glucose, insulin, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, total and free testosterone, dehydroepiandrosterone sulfate, high-sensitivity C-reactive protein (hs-CRP), fibrinogen and ferritin were measured on the same day. Plasma samples for VEGF, ICAM-1, VCAM-1, E-selectin and MMP-9 were centrifuged shortly after collection and stored at –80°C until batch analysis by enzyme-linked immunosorbent assay (ELISA).

The methods and instruments used for each measurement are listed in Supplementary Table S1.

Ethical Approval

The study was approved by the Ethics Committee of Karadeniz Technical University Faculty of Medicine (Date: 29.06.2009, Approval No: 2009/87, Decision No: 33). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

Analyses were performed on the final participant-level dataset (20 per group, no missing values). Normality was assessed separately within each group using the Shapiro–Wilk test. Variables with $P > .05$ in all three groups were summarized as mean ± standard deviation; other variables were summarized as median (25th–75th percentiles). Homogeneity of variance was assessed using

median-centered Levene's test. Normally distributed variables were compared using one-way ANOVA when variances were homogeneous and Welch ANOVA otherwise. Non-normally distributed variables were compared using the Kruskal–Wallis test. Following significant omnibus tests, pairwise comparisons used pooled-variance *t* comparisons after standard ANOVA, Welch *t* comparisons after Welch ANOVA, and Dunn's test with correction for ties after the Kruskal–Wallis test. Bonferroni adjustment was applied to the three pairwise comparisons within each variable to control the family wise Type I error rate at 0.05; adjusted *P* values were compared with 0.05, equivalent to an unadjusted threshold of approximately 0.0167. No additional adjustment was applied across the different biomarkers, and these analyses were interpreted as exploratory. Associations between EPC counts and other variables were assessed using Spearman's rank correlation. All tests were two-sided.

Calculations were performed in IBM SPSS 23.0 (licensed by Karadeniz Technical University, Trabzon, Türkiye). No analysis adjusted for BMI was included in the primary biomarker comparisons.

Reporting Guidelines

This study was reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guideline for cross-sectional studies.

Results

Each group included 20 participants. Age did not differ significantly overall (*P = .070*). Body weight, BMI, fasting glucose, insulin and HOMA-IR were higher in IR-positive PCOS than in both IR-negative PCOS and controls after Bonferroni adjustment (Table 1). HDL-cholesterol was significantly lower in IR-positive PCOS than in controls, whereas triglyceride levels were higher than in both other groups. No significant differences in total cholesterol or LDL-cholesterol were found among the three groups. In the IR-negative group, no metabolic parameter differed from the control group (Table 1).

Total testosterone was higher in both PCOS groups than in controls. DHEAS was higher in IR-negative PCOS than in controls (adjusted *P = .026*). LH did not differ significantly among groups (*P = .074*). FSH, estradiol and free testosterone also did not differ significantly overall. hs-CRP, fibrinogen and ferritin were higher in IR-positive PCOS than in controls; ferritin was also higher than in IR-negative PCOS. E-selectin and MMP-9 were higher in IR-positive PCOS than in controls, whereas VCAM-1 was higher in IR-negative PCOS than in controls. ICAM-1 and VEGF did not differ significantly overall (Table 2). EPC counts did not differ significantly among the groups (Kruskal–Wallis H=5.335, *P = .069*). A weak positive correlation was found between EPC counts and FSH (Spearman rho=0.258, *P = .046*; exploratory); no other EPC correlation reached *P < .05*.

Discussion

PCOS, which affects one in ten women, is recognized not only as a reproductive disorder but as a chronic metabolic condition associated with a lifelong increased risk of cardiovascular disease.[1,4] IR is thought to play a central role in the pathogenesis of PCOS and is considered a major contributor to this increased cardiovascular risk.[3,4] IR has been proposed to impair EPC-mediated endothelial regeneration, which may contribute to atherosclerosis and cardiovascular disease risk.[6]

Circulating EPC counts did not differ significantly among the groups (*P = .069*). Because the study had limited power, this does not show that EPC number or function is preserved in PCOS. EPC counts were weakly correlated with FSH (rho=0.258, *P = .046*), but this was one of 24 unadjusted correlations and should be considered exploratory. Several previous studies have similarly reported non-significant EPC count differences. Rajendran et al. studied 12 obese and 12 normal-weight women with PCOS, whose testosterone levels were higher than those of controls, and observed no significant difference in EPC number compared with controls.[13] Similarly, in the largest cohort reported to date (109 women with PCOS and 133 controls, with higher BMI, fasting insulin, HOMA-IR and testosterone in the PCOS group), Chan et al. found no significant difference in EPC number.[14] In contrast, Dessapt-Baradez et al. evaluated EPC number and in-vitro tube formation

Table 1. Clinical And Metabolic Characteristics Of PCOS Patients And Controls

Parameter	IR-positive PCOS (*n* = 20)	IR-*n*egative PCOS (*n* = 20)	Con*t*rol (*n* = 20)	Overall *P* value	*P* adjusted
Age, y	23.00 ± 4.45	21.25 ± 2.59	23.90 ± 3.55	.070 (a)	NS
Body weight, kg	77.50 (64.25–102.00)	59.00 (54.25–72.50)	57.00 (53.00–63.00)	< .001 (k)	A–B: .015; A–C: < .001
BMI, kg/m²	31.92 ± 9.03	24.51 ± 4.82	22.20 ± 1.95	< .001 (w)	A–B: .009; A–C: < .001
Glucose, mg/dL	90.05 ± 6.22	84.30 ± 8.11	83.45 ± 5.29	.005 (a)	A–B: .025; A–C: .008
Insulin, µIU/mL	25.50 (14.25–33.00)	5.00 (3.25–6.75)	3.50 (2.00–6.00)	< .001 (k)	A–B: < .001; A–C: < .001
HOMA-IR	5.50 (3.00–7.00)	1.00 (1.00–1.00)	1.00 (0.00–1.75)	< .001 (k)	A–B: < .001; A–C: < .001
Total cholesterol, mg/dL	169.65 ± 27.06	159.15 ± 25.17	157.30 ± 25.75	.277 (a)	NS
LDL-C, mg/dL	98.00 (84.00–120.50)	97.50 (76.25–106.00)	93.50 (75.25–104.50)	.729 (k)	NS
HDL-C, mg/dL	45.55 ± 11.34	51.85 ± 8.43	55.05 ± 11.53	.020 (a)	A–C: .018
Triglycerides, mg/dL	117.00 (73.50–146.50)	60.00 (47.50–86.50)	67.00 (54.50–104.00)	.001 (k)	A–B: < .001; A–C: .044

Normally distributed variables are presented as mean ± standard deviation (SD) and non-normally distributed variables as median (Q1–Q3), where Q1 and Q3 denote the 25th and 75th percentiles, respectively. A, IR-positive PCOS; B, IR-negative PCOS; C, Control. Normality was assessed within each group using Shapiro–Wilk. a, One-way ANOVA; w, Welch ANOVA; k, Kruskal–Wallis. NS, Not significant. Pairwise P values are Bonferroni-adjusted within each variable: pooled-variance t comparisons after ANOVA, Welch t comparisons after Welch ANOVA, and tie-corrected Dunn comparisons after Kruskal–Wallis. Only significant comparisons following a significant omnibus test are listed. No multiplicity adjustment was applied across biomarkers.

Table 2. Hormonal Profile, Inflammatory And Endothelial Function Markers, And EPC In PCOS Patients And Controls

Parameter	IR-positive PCOS (*n* = 20)	IR-negative PCOS (*n* = 20)	Control (*n* = 20)	Overall *P* value	*P* adjusted
FSH, mIU/mL	5.95 ± 1.82	6.02 ± 1.57	6.45 ± 2.12	.651 (a)	NS
LH, mIU/mL	8.39 (5.41–13.80)	8.32 (4.36–13.69)	5.95 (4.15–6.72)	.074 (k)	NS
Estradiol, pg/mL	42.43 (34.89–63.86)	44.81 (34.99–62.04)	47.66 (33.53–88.93)	.931 (k)	NS
Total testosterone, ng/mL	0.45 (0.32–0.61)	0.45 (0.37–0.87)	0.24 (0.20–0.31)	< .001 (k)	A–C: .005; B–C: < .001
Free testosterone, ng/dL	1.55 ± 0.86	1.64 ± 0.83	1.32 ± 0.55	.391 (a)	NS
DHEAS, µg/dL	234.5 (176.50–303.50)	244.50 (201.50–330.25)	187.00 (152.00–231.50)	.029 (k)	B–C: .026
hs-CRP, mg/dL	0.30 (0.30–0.62)	0.30 (0.30–0.30)	0.30 (0.30–0.30)	.025 (k)	A–C: .024
Fibrinogen, mg/dL	358.80 ± 70.97	313.85 ± 64.64	306.10 ± 48.32	.020 (a)	A–C: .028
Ferritin, ng/mL	37.65 (23.47–65.54)	23.54 (14.13–26.88)	19.29 (13.66–29.64)	.009 (k)	A–B: .027; A–C: .022
ICAM-1, pg/mL	1189.20 ± 487.92	889.50 ± 650.53	927.00 ± 380.65	.135 (w)	NS
VCAM-1, ng/mL	639.20 ± 190.42	743.10 ± 257.33	538.45 ± 116.41	.006 (w)	B–C: .010
E-selectin, pg/mL	18754.70 ± 9054.48	16435.95 ± 10667.13	10158.90 ± 4645.04	.001 (w)	A–C: .002
MMP-9, pg/mL	3857.50 ± 1318.68	3378.75 ± 1151.92	2709.40 ± 873.68	.008 (a)	A–C: .006
VEGF, pg/mL	1504.50 (1023.03–1728.00)	1139.00 (765.25–2102.25)	1120.50 (814.00–1513.25)	.399 (k)	NS
EPC, per 100,000	3.50 (2.00–6.00)	2.00 (1.00–3.75)	3.00 (2.00–6.75)	.069 (k)	NS

FSH, Follicle-stimulating hormone; LH, Luteinizing hormone; DHEAS, Dehydroepiandrosterone sulfate; hs-CRP, High-sensitivity C-reactive protein; ICAM-1, Intercellular adhesion molecule-1; VCAM-1, Vascular cell adhesion molecule-1; MMP-9, Matrix metalloproteinase-9; VEGF, Vascular endothelial growth factor; EPC, Endothelial progenitor cell; NS, Not significant. Normally distributed variables are presented as mean ± standard deviation (SD) and non-normally distributed variables as median (Q1–Q3), where Q1 and Q3 denote the 25th and 75th percentiles, respectively. A, IR-positive PCOS; B, IR-negative PCOS; C, Control. Normality was assessed within each group using Shapiro–Wilk. a, One-way ANOVA; w, Welch ANOVA; k, Kruskal–Wallis. Pairwise P values are Bonferroni-adjusted within each variable: pooled-variance t comparisons after ANOVA, Welch t comparisons after Welch ANOVA, and tie-corrected Dunn comparisons after Kruskal–Wallis. Only significant comparisons following a significant omnibus test are listed. No multiplicity adjustment was applied across biomarkers.

in 14 non-obese women with PCOS; EPC number was significantly lower in the PCOS group compared with controls, and in-vitro tube formation was impaired, leading the authors to conclude that vascular repair is compromised in PCOS.[11] Bairagi et al. found significantly lower fasting CD133+, CD34+ and CD133+CD34+ cell counts in non-classic, non-hyperandrogenic amenorrheic PCOS patients compared with controls; after a 75-g oral glucose load, the increase in CD133+ cells was markedly weaker in amenorrheic subjects than in controls, and no increase in CD133+CD34+ cell number was observed.[12] In a recent, large case-control study of 84 women with PCOS and 76 controls, Zhang et al. showed that although EPC proliferative capacity was not significantly reduced, EPC migration and tube-formation capacity were significantly impaired in PCOS, an effect linked to up-regulation of miRNA-339-5p and consequent suppression of the PI3K/AKT and SIRT1/PGC-1α signaling pathways.[15] This finding suggests that, even when circulating EPC number does not differ, the functional, reparative capacity of these cells may be impaired.

Differences in androgen levels between cohorts may contribute to the inconsistent EPC findings across studies. In our study, as in those of Rajendran and Chan, serum total testosterone was significantly elevated in PCOS patients regardless of IR status, whereas in the study by Bairagi et al., which reported reduced EPC number, there was no clinical or biochemical evidence of hyperandrogenemia. Androgens are known to stimulate erythropoiesis.[23] It can be hypothesized that a similar stimulatory effect on CD34+/CD133+ progenitor cells might offset IR-related suppression of EPC mobilization. This hypothesis is speculative: EPC function, androgen action and the duration of IR were not assessed in our study.

Our findings indicate an inflammatory and endothelial-activation biomarker profile that was observed predominantly in the IR-positive group, which also had a higher BMI. hs-CRP levels were elevated in the IR-positive group, consistent with the literature[17,18] Similarly, fibrinogen and ferritin levels, additional markers of low-grade inflammation, were also elevated in our IR-positive group, consistent with previous national and international studies.[24,25] These unadjusted comparisons do not establish an independent effect of IR. Serum MMP-9 was significantly elevated in our IR-positive group, consistent with similar studies in the literature;[20,21] elevated MMP-9 has been suggested to promote atherosclerotic plaque development.[20,21] MMP-9 activation is an essential step in EPC mobilization from the bone marrow. One speculative interpretation of elevated MMP-9 with an EPC number that did not differ significantly from controls is that mobilization signaling is not impaired in early PCOS; this was not tested here, and functional assays are needed to evaluate EPC migration, adhesion and integration into injured endothelium.

In our IR-positive group, E-selectin was significantly higher than in controls, consistent with the literature,[17] whereas ICAM-1 and VCAM-1 did not differ significantly from controls. In the IR-negative group, VCAM-1 was significantly higher, whereas E-selectin did not differ significantly. This may indicate that endothelial adhesion-molecule activation in PCOS is not explained by IR alone; hyperandrogenemia-related endothelial activation is one possibility,[19] but was not tested here.

Serum VEGF did not differ significantly between either PCOS group and controls in our study; this is consistent with the heterogeneous VEGF findings reported in the PCOS literature, which may reflect differences in BMI-matching and phenotype composition between cohorts.

Taken together, our findings describe an inflammatory and endothelial-activation biomarker profile in young, newly diagnosed, treatment-naïve women with PCOS, predominantly in the IR-positive group, without a significant difference in circulating EPC number. Because BMI was higher in this group, the contributions of IR and adiposity cannot be separated. A short duration of IR exposure, the absence of overt hyperglycemia or a stimulatory androgen effect on EPCs are possible but untested explanations for the EPC findings.

Limitations

This study has several limitations. First, the sample was small and no a priori sample size calculation was performed. With 20 participants per group, the study had limited power, so the absence of a significant EPC difference does not exclude a moderate difference. Second, BMI was higher in the IR-positive group and the groups were not matched for BMI; no adjusted analysis was performed, so the effects of IR and adiposity on the inflammatory and endothelial markers cannot be separated. Third, Bonferroni correction was applied to the three pairwise group comparisons within each variable, but no additional multiplicity correction was applied across biomarkers or to the correlation analyses. Accordingly, these analyses should be considered exploratory, and borderline statistically significant findings should be interpreted cautiously because of the risk of Type I error. Fourth, only surrogate biochemical markers were measured, not clinical cardiovascular outcomes or atherosclerosis, and EPC evaluation relied on surface-marker flow cytometry rather than functional assays. The cross-sectional design does not allow assessment of changes over time. Finally, the participants were young, newly diagnosed, treatment-naïve women from a single center, and those with established cardiovascular risk factors or comorbidities were excluded; the findings should not be generalized to older women, women with established metabolic disease, or other PCOS phenotypes. Larger multicenter studies with functional EPC assays and longer follow-up are needed.

Conclusion

In this cross-sectional study, inflammatory and endothelial-activation markers were predominantly increased in the IR-positive PCOS group, which also had a higher BMI; the design does not allow the contributions of IR, BMI and other metabolic features to be separated. Circulating EPC number did not differ significantly between groups.

Declarations

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent

Written informed consent was obtained from all individual participants included in the study.

Data Availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

The authors declare no conflict of interest.

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Author Contributions (CRediT Taxonomy)

Conceptualization: H.Ö.E., Ö.Ü.
Methodology: H.Ö.E.
Validation: M.S., A.Ö.
Formal Analysis: Ö.Ü.
Investigation: N.U.
Resources: A.Ö., M.S.
Writing – Original Draft Preparation: Ö.Ü.
Writing – Review & Editing: H.Ö.E., C.E.
Visualization: Ö.Ü.
Supervision: H.Ö.E.
Project Administration: H.Ö.E., Ö.Ü.
All authors have read and approved the final version of the manuscript.

AI Usage Disclosure

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Abbreviations

BMI: Body mass index
CVD: Cardiovascular disease
DHEAS: Dehydroepiandrosterone sulfate
ELISA: Enzyme-linked immunosorbent assay
EPC: Endothelial progenitor cell
FSH: Follicle-stimulating hormone
HDL: High-density lipoprotein
HOMA-IR: Homeostasis model assessment of insulin resistance
hs-CRP: High-sensitivity c-reactive protein
ICAM-1: Intercellular adhesion molecule 1
IR: Insulin resistance
LDL: Low-density lipoprotein
LH: Luteinizing hormone
MMP-9: Matrix metalloproteinase 9
PCOS: Polycystic ovary syndrome
STROBE: Strengthening the reporting of observational studies in epidemiology
VCAM-1: Vascular cell adhesion molecule 1
VEGF: Vascular endothelial growth factor
VEGFR-2: Vascular endothelial growth factor receptor 2

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