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ORIGINAL ARTICLE

Endothelial cell-specific-molecule-1 (endocan) levels in women with premature ovarian insufficiency: a prospective comparative study

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ABSTRACT

There is an increased risk of cardiovascular disease in women with premature ovarian insufficiency (POI). A relationship between cardiovascular disease and endocan levels has been shown. Endocan is a marker that is prominent in many diseases caused by endothelial dysfunction and can be measured in the blood. POI is also associated with endothelial dysfunction. The causes of POI include chromosomal and genetic defects, autoimmune processes, chemotherapy, radiation, infections and surgery, but many are unidentified (idiopathic). This study aimed to evaluate serum endocan levels in women with idiopathic POI. The blood for analysis was obtained at the early follicular phase of the menstrual cycle and endocan levels were measured using a commercially available enzyme-linked immunosorbent assay kit. There were 38 patients with idiopathic POI in the study group and 39 healthy subjects in the control group. The median ages of the women were not significantly different between the groups 34 [7] years vs. 34 [7] years, respectively ($p = .862$). The median endocan level was not different in the POI and control group 769 [727] vs. 1077 [403] pg/mL, respectively ($p = .603$). Endocan is not associated with the cardiovascular diseases risk linked with endothelial dysfunction in idiopathic POI.

Clinical trial number: NCT03932877 (Clinicaltrials.gov)

KEYWORDS

Anti-mullerian hormone; cardiovascular diseases; endothelial dysfunction; infertility; inflammation; premature menopause; premature ovarian failure

IMPACT STATEMENT

- **What is already known on this subject?** There is an increased risk of cardiovascular disease in premature ovarian insufficiency (POI) due to the decreased level of oestrogen, which is linked with endothelial dysfunction.
- **What do the results of this study add?** This study showed that endocan is not associated with the cardiovascular disease risk linked with endothelial dysfunction in idiopathic POI.
- **What are the implications of these findings for clinical practice and/or further research?** A marker to be used to predict the risk of cardiovascular disease in patients with POI could facilitate in improving the quality of life of these patients. Moreover, advantageous and easy-to-measure markers are needed in larger sample studies to better understand the cardiovascular diseases risk in POI.

Introduction

Premature ovarian insufficiency (POI), defined as loss of ovarian function and subsequent amenorrhoea before the age of 40 years, has an estimated prevalence of 1% in the general population (Maclaran and Panay 2015). POI may be caused by chromosomal defects, genetic disorders, autoimmune diseases, infectious diseases or iatrogenic conditions. However, most cases of POI are still considered to be idiopathic. This condition, although similar in some aspects to low ovarian reserve (a condition strictly related to age whose main implications are reduced fertility and poor response to controlled ovarian stimulation), is related to fertility and shows a broad spectrum of symptoms and subsequent morbidity typical of oestrogen deficiency of post-menopausal women (Maclaran and Panay 2015; Chern et al. 2018; Lin et al. 2018). Early diagnosis is a fundamental step in starting a correct management, especially because POI is associated with an increased risk for cardiovascular diseases (CVDs). Ossewaarde et al.

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described a 2% reduction in mortality from ischaemic heart disease with each increasing year of age at menopause (Ossewaarde et al. 2005; Quinn and Cedars 2018). CVDs might be attributed to the early onset of vascular endothelial dysfunction, associated with sex steroid deficiency (Quinn and Cedars 2018). Low anti-mullerian hormone levels and low ovarian reserve have been associated with preeclampsia, which represents a specific risk factor for CVDs (Woldringh et al. 2006). Oestrogen replacement therapy in women with POI may decrease cardiovascular risk, probably through a direct effect on the vascular epithelium (Quinn and Cedars 2018).

Endothelial cell-specific-molecule-1 (endocan, ESM-1) is a soluble proteoglycan expressed by the vascular endothelium. It is a marker for vascular pathologies, and it is strongly associated with vascular endothelial dysfunction, inflammation, and atherosclerosis (de Kat et al. 2017; Kalantaridou et al. 2006). Interestingly, different studies associated high levels of endocan to preeclampsia (Schuitemaker et al. 2018) and also another gynaecologic condition associated with endothelial dysfunction: polycystic ovary syndrome (Pan et al. 2017). There is no normal range for endocan levels in healthy women in the literature.

No published studies in the literature have investigated blood endocan levels in women with POI. Therefore, considering the high risk of CVDs in patients affected by POI and the importance of an early diagnosis of this endothelial disease, we aimed to investigate the possible changes of endocan concentrations in the serum of women affected by idiopathic POI.

Materials and methods

Study design

This was an observational prospective cohort study conducted at the Obstetrics and Gynaecology Department of Cengiz Gokcek Obstetrics and Children's Hospital between July and December 2018. The study was conducted in the largest city of the Eastern region of Turkey with a population of 3 million people. In our hospital, more than 20,000 women are accepted for gynaecologic examinations annually (Ovayolu and Guler 2020). The study consecutively recruited subjects with idiopathic POI and healthy patients (control group). All patients gave their oral and written informed consent before being included in the study. The protocol was approved by the Ethics Committee for Clinical Research of Gaziantep University (reference number: 2018/64). The study strictly adhered to the principles of the Declaration of Helsinki.

Inclusion and exclusion criteria

The study included patients with the diagnosis of idiopathic POI. The diagnosis of POI was made in accordance with the European Society of Human Reproduction and Embryology guidelines. The diagnosis of POI is usually made in women aged <40 years through a combination of a 4–6-month period of oligomenorrhea/amenorrhoea and two measurements of elevated follicle-stimulating hormone (FSH) (at least 25 mIU/mL). In the POI group, FSH measurements were repeated with 4-week intervals (Webber et al. 2016). Women aged between 19 and 39 years were included. A volunteer group of healthy women who visited the gynaecology clinic for routine examinations and women who were admitted for pre-pregnancy tests were invited randomly to this research as a control group. Healthy women, who returned during their early follicular phase of the menstrual cycle, were recruited as the control group subjects. All volunteers for the control group had regular menstrual cycles and no concomitant health problems. The exclusion criteria for the study group were as follows: women with evidence of a karyotypic, metabolic, toxic, or iatrogenic cause of ovarian insufficiency and any women who used any medication for POI treatment (e.g. hormone therapy, medicinal herb), women who have had more than 12 months of amenorrhoea, women who had any infection, and any CVDs.

Data collection and study intervention

At enrolment, for both groups, data were collected regarding age, height, weight, body mass index, age of menarche, obstetric history, history of smoking, history of regular exercise, and family history of POI. The study defined that the POI period was the time from the first diagnosis of POI to the evaluation at our institute and recruitment into the study. At enrolment, all patients underwent vaginal ultrasonography for the assessment of antral follicle counts (AFC) and a venous blood sample was taken from the antecubital veins for measuring serum concentrations of endocan, FSH, oestradiol, anti-mullerian hormone, and full blood count. In control subjects, AFC was assessed and venous blood samples were collected during the early follicular phase of the menstrual cycle (2nd to 5th days) in the morning (between 08.00 and 09.00 AM). Anti-mullerian hormone was not measured in the control group. AFCs were assessed by the same author using vaginal ultrasonography (Mindray DC-7T ultrasound device, Shenzen-Mindray Bio-Medical Electronics Co. Ltd., China). Blood samples were separated by centrifugation for 10 minutes at 1500 g after clotting for 30 minutes at room temperature. The serum samples were subsequently stored in aliquots at $-80\,^{\circ}C$ prior to the analysis of endocan. Serum endocan levels were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit, which is produced to detect human endocan levels with high sensitivity and specificity (Elabscience Biotechnology Inc., Houston, TX, USA). The endocan measurements were performed in accordance with company's protocol. The kit, human endocan ELISA kit, uses the sandwich ELISA principle. A biotinylated detection antibody specific for human endocan and avidin-horseradish peroxidase conjugate were used in the measurement. The procedure was processed using BioTek ELx800 microplate readers and the Gen5 software programme. Spectrophotometry at a wave length of 450 ± 2 nm was used in the detection of optical density, which is proportional to the concentration of human endocan level. The

intra- and inter-assay variation coefficients were 6.36% and 6.09%, respectively.

Outcome measures of the study

The primary outcome measure in this analysis was to compare endocan levels in the idiopathic POI group and control group. The secondary outcome measure was to compare endocan levels in the study group for the POI period. The tertiary outcome measure was to compare the endocan levels in both groups according to those who did and did not give birth.

Statistical method

To detect significant difference between the groups according to endocan levels with a moderate effect size (Cohen's $d = 0.7$), the minimum required sample size was estimated as 34 for each group ($\alpha = 0.05$, $1\text{-}\beta = 0.80$). Power analysis was performed by using the G*Power package version 3.1. The normality of distribution of continuous variables was tested using the Shapiro-Wilk test. To compare numerical variables between two groups, Student's t-test (for normal variables) or the Mann-Whitney U test (for non-normal variables) was performed. Frequency, percentage (%) for categorical variables and mean ± standard deviations (mean ± SD) and median [inter-quartile range] are given as descriptive statistics for numerical variables. Statistical analysis was performed using the SPSS for Windows version 25.0 software package, and p values $<.05$ were accepted as statistically significant (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.).

Results

Seventeen patients with POI who presented to our clinic were not recruited [women with evidence of a karyotypic, metabolic, toxic, or iatrogenic cause of ovarian insufficiency ($n = 5$), women who used any medication for POI treatment (e.g. hormone therapy, medicinal herb,) ($n = 10$), and women with infection ($n = 1$) and any CVDs ($n = 1$)]. In this study, eighty women were recruited in the idiopathic POI and control group. After that, one patient (1.25%) in the idiopathic POI group was excluded from the study because they declined to participate. One patient (1.25%) in the idiopathic POI group and one patient (1.25%) in the control group had missing variables. All of these patients were also excluded from the study. The median FSH level was significantly higher in the POI group than in the healthy controls 62.5 [49] vs. 6 [2] mU/mL, respectively ($p = .001$). The median AFC was significantly lower in the POI group than in the healthy controls 3 [3] vs. 21 [4], respectively ($p = .001$). The two cohorts were comparable in terms of age at enrolment 34 [7] vs. 34 [7] years, respectively ($p = .862$), age of first menstruation 13 [2] vs. 13 [2] years, respectively ($p = .932$,), history of smoking or active smoking ($n = 8$ vs. $n = 12$, $p = .331$, respectively), and regular physical activity ($n = 9$ vs. $n = 3$, $p = .053$, respectively). Body mass index and family history of POI were statistically higher in the POI group (26.24 ± 4.66 vs. 24.03 ± 2.96 kg/m^2, $p = .015$; $n = 10$ vs. $n = 3$, $p = .029$, respectively). Parity, number of pregnancies and live births were statistically higher among the control subjects (Table 1). In the POI group, the median anti-mullerian hormone value was 0.1 (min-max, 0.01–0.5) ng/mL, and the median interval time (POI period) between the diagnosis of POI and enrolment was 2.0 (min-max, 0–20) years. Hormonal values (oestradiol and FSH) and AFCs were statistically different between the two cohorts. Haemoglobin and haematocrit values were statistically higher in the POI group (Table 2). The median endocan concentrations were not significantly different between the groups 769 [727] vs. 1077 [403] pg/mL, respectively ($p = .603$). The mean values of endocan levels of patients with POI periods of 0–2 years ($n = 22$) and those with more than 10 years ($n = 7$) were compared. There was no statistically significant correlation between POI periods and endocan levels ($r = -0.027$, $p = .874$). The women were categorised as those who had given birth and those with no children, and their mean endocan levels were compared (Table 3). Then, the POI group and the control group were categorised

Table 1. Demographic characteristics of premature ovarian insufficiency and control groups.

Variables	POI ($n = 38$)	Control ($n = 39$)	p
BMI (kg/m^2)†	26.24 ± 4.66	24.03 ± 2.96	.015*‡
Age (years)	34 [7]	34 [7]	.862§
Age of menarch (years)	13 [2]	13 [2]	.932§
Number of pregnancy	0 [2]	2 [2]	.001*§
Parity	0 [2]	2 [1]	.002*§
Live birth	0 [2]	2 [1]	.002*§

POI: premature ovarian insufficiency group; BMI: Body mass index; †Mean ± SD, ‡Student's t-test, §Mann-Whitney U test, *Significant at 0.05 level.

Table 2. Laboratory analyses in premature ovarian insufficiency and control groups.

Variables	POI ($n = 38$)	Control ($n = 39$)	p
FSH (mU/mL)	62.5 [49]	6 [2]	0.001*‡
Oestradiol (pg/mL)	17 [43]	48 [42]	0.001*‡
AFC	3 [3]	21 [4]	0.001*‡
Haemoglobin (g/dL)	13 [1]	12 [2]	0.007*‡
Haematocrit (%)	38 [3]	36 [4]	0.001*†
Platelets ($\times 10^3$/μL)	268 [96]	282 [75]	0.454‡
WBC (μL/mL)	6 [2]	6 [2]	0.149‡
Endocan (pg/mL)	769 [727]	1077 [403]	0.603‡

POI: premature ovarian insufficiency group; FSH: Follicle-stimulating hormone; AFC: Antral follicle count; WBC: White blood cells, †Student's t-test, ‡Mann-Whitney U test, *Significant at 0.05 level.

Table 3. Endocan levels in women who had and had not given birth.

Variable	Given birth ($n = 54$)	Not given birth ($n = 23$)	P
Endocan (pg/mL)	1067 [677]	814 [604]	0.876

Mann-Whitney U test, *Significant at 0.05 level.

Table 4. Endocan levels in women who had and had not given birth in the premature ovarian insufficiency and control group.

	Variable	n	POI	p	n	Control	p
Given birth	Endocan (pg/mL)	17	1043 [925]	.772	37	1069 [439]	.132
Not given birth	Endocan (pg/mL)	21	778 [635]		2	1202	

POI: premature ovarian insufficiency group, Mann-Whitney U test, *Significant at 0.05 level.

according to births and their mean endocan levels were compared (Table 4). No significant differences were found in either comparison.

Discussion

The study aimed to investigate endocan as a marker that might predict CVDs risk in patients with POI. However, endocan was not found different between the groups. Therefore, although serum endocan levels have been associated with several endothelial dysfunction-related diseases, it was not associated with endothelial dysfunction in idiopathic POI in this study. Also, endocan was not associated with POI period and birth numbers.

Patients with POI may have some important risk factors for the development of CVDs: endothelial dysfunction, abnormal lipid profile, insulin resistance, and insulin action disturbances (Podfigurna et al. 2018). The reason why women with POI have early-onset vascular endothelial dysfunction is associated with sex steroid deficiency. Cyclical oestrogen and progestogen therapy has been shown to restore endothelial function in these young women. Any hormonal treatments, alternative and complementary treatments in patients with POI may have potential effects on endocan levels (Kalantaridou et al. 2006). When POI is not treated, there may be a reduction in life-span due to cardiovascular problems. Therefore, the following are proposed to reduce the risk of CVDs in POI: smoking cessation, regular exercise (involving weight-bearing exercise), and maintaining a healthy weight (Amagai et al. 2006; Hong et al. 2007; Webber et al. 2016). For the relationship between POI, CVDs, and vascular endothelial cells (or metabolites), there are insufficient studies in the literature about markers that provide foresight and the changes of these markers with treatment.

Endocan is an endothelial dysfunction marker (Aparci et al. 2015; Zhao et al. 2018). Endothelial dysfunction is an important component of preeclampsia and hypertension and it is reported that endocan is increased in these conditions (Balta et al. 2014; Adekola et al. 2015; Balta et al. 2015). Also, vascular endothelial dysfunction is an early marker of CVDs (Gimbrone and García-Cardeña 2016). It can be hypothesised that because patients with POI have high CVD risk and endothelial dysfunction, endocan levels may be different in this group of patients and may have a predictive value. However, endocan levels in the POI group showed no statistically significant difference in this study population. However, endocan could be significant in different POI patient populations.

In the literature search, several studies tried to investigate the link between POI and cardiovascular risk markers. Kebabçılar et al. found that D-dimer showing fibrin turnover was higher in women with POI ($p < .001$) (Kebapcilar et al. 2013). This suggests that vascular (endothelial), thromboembolic events may be effective in POI. Sanverdi et al. also found that neutrophil/lymphocyte ($p = .001$) and mean platelet volume/lymphocyte ($p = .003$) ratios were significantly higher in POI. A reduction of oestrogen levels leads to an increase in pro-inflammatory processes with the increase of pro-inflammatory active metabolites. This process can be corrected with oral oestrogen treatment (Sanverdi et al. 2018). Contrary to these articles, a more recent study showed that there was no increase in CVD risk in patients with POI (Gunning et al. 2020). When the results of this new research and our results are evaluated together, patients with POI (aged <40 years) might not have CVD risk like middle-aged women with POI. Accordingly, in this study, endocan levels secreted from the vascular endothelium in the idiopathic POI group showed no statistically significant difference. Otherwise, there may be other systemic vascular markers involved in cardiovascular endothelial dysfunction in patients with POI.

There are strengths of this study. The women participating in the study had idiopathic POI and had not received treatment. The relationship between smoking and CVDs is clear, and smoking status was similar between the groups in this study. Exercise in also important in CVDs. In this study, there was no statistical difference between the groups in terms of those who exercised. Therefore, the effects of smoking and exercise were reduced in both groups. This study gives a new idea regarding the development of a predictive marker for CVDs in POI. After this study, this new area of research can attract the attention of many researchers. Also, we brought a different perspective to POI by comparing women with POI who did and did not give birth. However, there are some limitations of the present study. This non-interventional study was not a multicenter study. Endocan levels were measured as an inflammatory marker, we did not measure other systemic inflammatory markers, angiogenic factors and CVD tests (e.g. cardiac troponins and creatine kinase MB), which may differ in POI.

In this study, endocan was not different in the study group. However; in addition to endocan, other vascular endothelial markers, systemic inflammatory markers, angiogenic factors and CVD tests are also worth investigating in women with POI with a high number of patients. In this way, physicians who have predictive tests could be successful in reducing the negative effect of CVDs in patients with POI.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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