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The importance of serum estrone level in cases of chronic venous insufficiency in the lower extremity

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ABSTRACT

Aims: Chronic venous insufficiency (CVI) is a condition characterized by abnormal venous flow dynamics in the lower limbs and is associated with various risk factors such as pregnancy, age, obesity, and high estrogen states. One of these estrogens, estrone, is known to have cardioprotective effects. The study aimed to evaluate the relationship between estrone levels in women with CVI and healthy women.

Methods: Clinical and laboratory data from 39 women with CVI and 31 healthy women without CVI were collected. All participants underwent spectral Doppler examinations and combined B-mode imaging to assess the severity of CVI.

Results: The results showed a statistically significant increase in the diameter of the vena saphenous magna in the CVI group compared to the healthy control group ($p<0.05$). However, there were no significant differences in estrone levels between the two groups. Besides, significant correlations were observed between estrone levels and age (r: -0.351; p=0.028), BMI and age(r: 0.374; p=0.019), and BMI and abdominal circumference (r: 0.700; $p<0.001$) in the CVI group.

Conclusion: Our study suggests that estrone levels may have a protective effect on CVI pathogenesis. The observed effect of estrone on women with CVI may be attributed to its different receptor-level effects compared to estradiol. Further research is necessary to fully elucidate the contribution of estrone to CVI and its underlying mechanisms.

Keywords: Chronic venous insufficiency, estrone, cardioprotective effect, estrogen

INTRODUCTION

Chronic venous insufficiency (CVI) of the lower limbs coincides with a broad clinical range, ranging from asymptomatic but aesthetic abnormalities to severe symptoms.[1] Abnormal venous flow dynamics of the lower limbs are observed in approximately half of the individuals, albeit the estimated prevalence of CVI may vary according to population studies.[2] The risk factors for CVI include prior venous thrombosis, obesity, smoking, family history, pregnancy, advancing age, prolonged standing, a sedentary lifestyle, and high estrogen.[3,4] The presence of varicose veins, skin changes, swelling, leg discomfort, and or ulceration are well-characterized clinical features of CVI. Patients suffering from varicose veins could experience tenderness as a result of venous distension. Varicose veins are characterized by their superficial nature, as well as their bulging and dilated appearance. These veins typically have a diameter of at least 3 mm and exhibit a gradual increase in tortuosity and enlargement over time. A comprehensive physical examination and medical history are essential for establishing a correct diagnosis of CVI. Physical examination should be performed in the upright position to allow maximal distension of the veins. Venous duplex ultrasonography (VDU) is the most prevalent method for diagnosing CVI and provides etiological and anatomical data.[5] VDU provides a combined spectral Doppler and B-mode imaging to detect the presence of venous reflux and insufficiency. The use of color-assisted VDU can help detect venous flow patterns and flow direction. Venous reflux is defined as any noticed reverse flow toward the foot. The Valsalva maneuver, which increases intra-abdominal pressure, can be used to confirm flow characteristics, valve functions, and venous reflux in the central vessels. Venous reflux is revealed by prolonged reverse flow following augmentation.

CVI is known to be associated with high estradiol levels during pregnancy.[6] A study has demonstrated the potential involvement of endogenous estrogens in the development of CVI during the menopausal period.[7]

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The ovaries produce and release two main estrogens, estrone (E1) and estradiol (E2), into circulation. Adipose tissue is also an important source of endogenous estrogens.[8] The peripheral aromatization of testosterone and androstenedione is the main source of circulating E1.[9] Molecular-level studies on estrone have shown potential cardioprotective effects, including vasodilation.[10-12]

In our study, we aimed to evaluate the relationship between estrone levels in women with CVI during the reproductive period and healthy women.

METHODS

Ethical Statement

The study was carried out with the permission of Medicana International İstanbul Hospital Ethics Committee (Date: 03.03.2023, Decision No: 001/2023). All methods were handled in accordance with the regulations and relevant guidelines (principles of the Declaration of Helsinki). Written informed consent was obtained from all of the patients.

Study Design

The clinical and laboratory results of 39 women presenting with CVI in the lower extremity and 31 healthy women without venous insufficiency were evaluated at the Cardiovascular Surgery outpatient clinic of Medicana International İstanbul Hospital through March 2023.

All patients included in the study underwent combined B-mode imaging and spectral Doppler examinations. The diameter of the vena saphena magna at the level of the saphenofemoral junction in the study group was found to be 7.56±0.53 mm, and spectral Doppler ultrasonography revealed stage 3 or 4 insufficiencies in all cases, meeting the criteria for surgical intervention. The control group consisted of asymptomatic individuals. The vena saphena magna diameter at the saphenofemoral junction in the control group was 3.35±0.24 mm, and the spectral Doppler ultrasonographic evaluations indicated no insufficiency (level 0).

Estrone levels were measured between the 2nd and 5th days of menstruation, corresponding to the early follicular phase of the menstrual cycle, in all women included in the study. However, women in the premenarchal and menopausal periods, as well as pregnant women, and those who were using estrogen, progesterone, or gonadotropin-derived hormone replacement for any reason were excluded from the study. All women were required to have passed a minimum of one year since their most recent pregnancy and have regular menstrual cycles. None of the women had any chronic illness that could affect estrone levels or facilitate the formation of varices.

The age range of the women included in the study was 21-47. The demographic data such as age, BMI, waist circumference measurement, gravidity, parity, and smoking status were evaluated.

Blood samples from both patients and controls were collected in the morning between 9-12 am. The blood collection protocol was designed to align with the early follicular phase of the menstrual cycle, between the 2nd and 5th days of menstruation, to eliminate variations in estrone hormone levels due to different cycle days. The serum of these samples was separated through centrifugation at 3500 rpm for 10 min and was stored in eppendorf tubes at -20°C until further analysis. The Estrone levels in the collected serum samples were measured.

Measurement of Estrone levels

BT-LAB, Human Estrone, E1 ELISA KIT (Cat. No. E3035Hu, Bioassay Technology Laboratory, China) was used to determine serum estrone levels. The coefficients of inter- and intra-assay variations were <10% and <8%, respectively. Results are given as pg/ml.

Statistical Analysis

SPSS program (Version 21) (IBM, USA) was used for statistical analysis. The Kolmogorov-Smirnov test was used to analyze the distribution of all parameters. For normally distributed continuous variables, the results were reported as means standard deviations. The statistical significance of the differences between the means was analyzed by the student's t-test. Pearson's correlation analysis was performed for the correlation analysis. A p-value below 0.05 was accepted to be significant.

RESULTS

The women included in the study were divided into two groups according to the presence of severe CVI in the lower extremities. Age, body mass index, abdominal circumference, gravida, parity, and smoking were recorded as demographic data for both groups (Table 1). There was no age bias between the groups (p>0.05, data not shown).

Table 1. The demographic data of subjects in the control and chronic venous insufficiency groups

The Demography	Controls (n=31)	Chronic venous insufficiency (n=39)	p value
Age (year) (mean±SD)	31.00±7.77	34.44±7.83	0.072
BMI (kg/m²) (mean±SD)	22.90±3.56	24.94±3.87	0.026
Abdominal circumference (cm) (mean±SD)	91.50±9.57	93.73±5.80	0.394
Gravida (mean±SD)	0.71±1.16	1.05±1.19	0.216
Parity (mean±SD)	0.61±1.02	0.90±0.96	0.153
Smoking (n (%))	12 (38.7 %)	7 (17.9 %)	0.052

BMI: Body mass index; VSM: Vena saphena magna; SD: Standard deviation

As the primary results of the study were evaluated, the increase in the diameter of the vena saphenous magna in the CVI group compared to the control group was statistically significant. However, no significant differences were found between the groups in terms of estrone levels (Table 2).

Table 2. Clinical data results of the subjects included in examined groups

Parameters	Controls (n=31)	Chronic venous insufficiency (n=39)	p value
Estrone (ng/L) (Mean±S.D.)	688.19±376.00	528.80±319.82	0.065
VSM diameters (mm) (Mean±S.D.)	3.35±0.24	7.56±0.53	0.001

VSM: Vena Saphena Magna

Besides, a significant correlation between estrone levels and age (r: -0.351; p=0.028), between BMI and age (r: 0.374; p=0.019), and abdominal circumference (r: 0.700; p<0.001) were determined in the CVI group. No significant correlation was found between estrone levels and VSM diameters (Table 3).

Table 3. The Pearson correlation analysis results of the subjects in the chronic venous insufficiency group

		Estrone	BMI	Abdominal circumference	VSM diameters
Age	r	-0.351*	0.374*	0.250	0.087
	p	0.028	0.019	0.124	0.598
Estrone	r	-	-0.138	-0.014	-0.217
	p		0.402	0.933	0.185
BMI	r	-0.138	-	0.700**	0.234
	p	0.402		0.000	0.152
Abdominal circumference	r	-0.014	0.700**	-	-0.137
	p	0.933	0.000		0.406

Statistically significant parameters were shown in bald; r: Pearson correlation coefficient; *: p<0.05; **: p<0.01

DISCUSSION

The presence and high levels of estradiol (increased female population, conditions such as pregnancy) are facilitating factors for the pathogenesis of CVI.[6,7] Despite a few studies suggesting the potential importance of estrogen in the pathogenesis of venous insufficiency, there is a lack of data regarding the significance of estrone levels. The presence of cardioprotective effects, including vasodilation, associated with estrone could explain possible mechanisms in CVI pathogenesis.

Although estrone and its precursor, estradiol, bind to the same receptor, the efficacy of estrone is 10 times lower compared to estradiol.[10-12] Nevertheless, the effects of estrone on both vessels and endothelium suggest that estrone alone may play a role in CVI pathogenesis.

The contribution of estrone to CVI pathogenesis has not yet been fully elucidated. However, based on existing literature, it has been proposed that estrone may contribute to CVI pathogenesis through the potent effect of estradiol and its conversion to estradiol.[13]

In our study, we found that estrone levels in women with CVI were lower compared to the control group, although the difference was not statistically significant. This finding contradicts the expected effect of estradiol.

The higher estrone levels in the control group compared to CVI patients suggest a possible protective effect of estrone in CVI pathogenesis. The observed effect on women with CVI can be explained by the different receptor-level effects of estrone and estradiol on the endothelium. A previous study, supporting our findings, suggested that estrone and estradiol have different effects and physiological impacts at the receptor level.[14]

Various molecular studies have reported increased sensitivity to estrogens at the receptor level in CVI patients.[15-17]

Another distinct finding of our study suggests that estrone, known to be primarily derived from adipose tissue and dramatically increased in postmenopausal periods, may have a protective effect on CVI.

In another study, a direct relationship between estrone and vasodilation and other endothelial functions was reported and low levels of estrone were associated with vascular dysfunction and increased risk of cardiovascular disease.[18] A study investigating the relationship between estrone and vasodilation reported that estrone mediates vasodilation through nitric oxide (NO) via cGMP activation.[19] Studies have shown that NO plays a vasoprotective role through its effects on vasodilation, regulation of leukocyte adhesion, regulation of vascular smooth muscle proliferation, and anticoagulant effects.[20] In another study of CVI, lower plasma NO levels were reported in CVI patients, contributing negatively to CVI pathogenesis.[21] Considering this information, the potential protective effect of estrone on CVI in our study may be explained through its action on NO.

CONCLUSION

However, further molecular-level studies are needed to understand the mechanisms induced by estrone binding to peripheral vascular structures.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Medicana International İstanbul Hospital Ethics Committee (Date: 03.03.2023, Decision No: 001/2023).

Informed Consent: All patients signed and free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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