Original Article

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The evaluation of C-reactive protein values in patients with primary chronic venous insufficiency

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ABSTRACT

Objectives: The aim of our study was to assess the alterations in serum C-reactive protein (CRP) values in patients with chronic venous insufficiency (CVI).

Patients and methods: Between June 2013 and November 2013, a total of 100 consecutive patients (50 males, 50 females; mean age 42±13 years; range, 21 to 61 years) who were admitted to the outpatient clinic with pain, prickle, paresthesia or night cramps were included in this study. The patients were divided into two groups. Varice group (n=50) consisted of isolated CVI patients (primary CVI) with a family history of varices and without a history of deep venous thrombosis. Non-varice group (n=50) consisted of patients who underwent non-venous pathologies-related surgical interventions previously or had no prior history of surgery. All patients underwent lower limb venous Duplex ultrasound examination bilaterally. Serum CRP and complete blood count examinations were performed and white blood cell (WBC) levels were assessed.

Results: There was no statistically significant difference between the varice group and non-varice group in terms of the mean CRP values (3.80±1.47 mg/L vs 4.74±3.86 mg/L, respectively; p=0.983). However, the mean WBC levels were statistically and significantly different between the groups (6966±1943/μL for varice group vs 8528±2767/μL for non-varice group, respectively; p<0.05).

Conclusion: Our study results suggest that CRP is not a valuable marker in the diagnosis of primary CVI.

Keywords: C-Reactive protein; inflammation; varice; venous insufficiency.

Chronic venous insufficiency (CVI) is a frequent disorder in which the primary reason is inadequate venous drainage in lower limbs affecting 50% of overall population.[1] Sex, race, family history, the number of partum, and lifestyle of individuals (e.g. standing or sitting position of daily workstyle) are some of the main reasons of CVI.[1] On the other hand, CVI may develop due to post-thrombotic syndrome (PTS) after deep venous thrombosis (DVT). Venous hypertension, impaired microcirculation, and alterations in the blood viscosity are the major factors in the pathogenesis of the disease.[2] A great amount of neutrophil and monocyte sequestration toward the vessel wall are observed during venous hypertension.[3] Venous valve deformation due to inflammation and ineffective fibrinolysis lay the groundwork for the CVI development.[4] However, the effect of inflammation on CVI has not been clearly understood, yet.[5]

The clinical signs of CVI varies from no-sign-and-symptom state to skin ulcers, and CVI is one of the leading reasons of skin ulcerations.[6] Therefore, CVI is assessed by the Comprehensive Classification System for Chronic Venous Disorders (CEAP) classification in which clinical findings (C), etiology (E), anatomical distribution (A), and physiological status (P) are scored all together.[1,5,7]

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Several studies have shown that diosmin + hesperidin combination having venotonic and anti-inflammatory effects relieves CVI symptoms and decreases microinflammation.[3,8] The effects of inflammation markers on etiopathogenesis are assessed in patients with PTS and DVT in many studies, but not in patients with isolated CVI without PTS or DVT.[3,7,9,10] In the present study, we aimed to assess the levels of an inflammatory marker, C-reactive protein (CRP), in patients with isolated CVI.

PATIENTS AND METHODS

Between June 2013 and November 2013, a total of 100 consecutive patients (50 males, 50 females; mean age 42±13 years; range, 21 to 61 years) who were admitted to the outpatient clinic with pain, prickle, paresthesia or night cramps were included in this study. An informed consent was obtained from each patient. The study protocol was approved by the local Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Exclusion criteria for both groups were as follows: use of anti-inflammatory drugs within the past week, any use of medications for CVI, previous history of DVT or pulmonary thromboembolism, patients with venous pathologies, patients at the Stage of C4, C5, and C6 clinically according to the CEAP classification, patients with venous obstruction according to the CEAP classification, ongoing infection, acute inflammatory and rheumatic diseases, acute myocardial infarction or any operation within the past six months, history of malignancy, left ventricular ejection fraction of less than 50%, pulmonary hypertension, and acute trauma.

The patients who met the inclusion criteria were divided into two groups. Varice group (n=50) consisted of patients who had no prior history of DVT and/or venous ulceration and were diagnosed with isolated CVI (primary CVI) by Duplex ultrasound. Non-varice group (n=50) included the patients with normal Duplex ultrasound findings without a prior surgery for venous or non-venous pathologies.

Bilateral lower limbs of all subjects were evaluated by Duplex ultrasound whether they had venous pathologies and they were classified using the CEAP classification based on the ultrasound findings. Blood samples were taken to immediately assess serum CRP values and complete blood count (CBC) without any delay.

Statistical analysis

Statistical analysis was performed using the Sigmastat Version 3.5 (Systat Software Inc., 2007, CA, USA). Continuous variables were presented in mean ± standard deviation (SD) and categorical variables were presented in frequency (%).Continuous variables did not show normal distribution according to the Kolmogorov-Smirnov test. Categorical variables were compared using the chi-square test. The Spearman's simple correlation analyses were performed to identify the association between continuous parameters, while the Mann-Whitney U test was used to compare continuous variables between the groups. A p value of less than 0.05 was considered statistically significant.

RESULTS

The mean age of the varice group was 42±13 years, while the mean age of the non-varice group was 42±12 years (p=0.836). The results of the patients in terms of the CEAP classification are shown in Table 1. There was no significant difference in terms of gender and smoking history between the groups (p=0.546 and p=0.118, respectively). Demographic, clinical, and laboratory characteristics of the patients are presented in Table 2. There was no significant difference between the groups in terms of CRP values (p=0.882). However, the mean WBC level of the non-varice group was found to be significantly higher than that of the varice group (p<0.01). In the varice group, we found no significant correlation between the CRP and WBC levels, while there was a significant correlation in non-varice group (p<0.05, r=0.349).

Table 1. CEAP classification of the patients

	n
Clinical classification	
C1	12
C2	20
C3	18
Etiologic classification	
Congenital	0
Secondary (post-thrombotic)	0
Primary	50
Anatomic classification	
Superficial veins	44
Perforator veins	2
Deep veins	4
Pathophysiologic classification	
Reflux	50
Obstruction	0
Reflux and obstruction	0

CEAP: Clinical-etiology-anatomy-pathophysiology.

Table 2. Demographic, clinical, and laboratory data of patients

	Varice group (n=50)			Non-varice group (n=50)		
	n	%	Mean±SD	n	%	Mean±SD
Age (year)			42±13			42±12
Gender						
Female	21			29		
Male	24			26		
Smoking	38	76		44	88	
Obesity (BMI >25 kg/m^2)	8			4		
Diabetes mellitus	7			11		
Family history	37			20		
Pregnancy	19			14		
Complaints at admission						
Leg pain	37			50		
Tingling in leg	12			21		
Nighttime leg cramps	32			4		
CRP (mg/L)			3.80±1.47			4.74±3.86
WBC (per µL)			6966±1943			8528±2766

SD: Standard deviation; BMI: Body Mass Index; CRP: C-reaktif protein; WBC: White blood cell.

DISCUSSION

In the present study, we assessed the alterations in serum CRP values in patients with CVI and we found that CRP was not a valuable marker in the diagnosis of primary CVI.

Chronic venous insufficiency is a multifactorial disease affecting approximately half of the population[1] in the literature, there have been several studies investigating the etiology of the disease; however, the researchers have mostly focused on CVI secondary to DVT. In a review, Smith and Golledge[11] reported that estradiol, homocysteine, and vascular endothelial growth factor were mostly investigated biomarkers in effort to find etiology of CVI. However, there is a limited number of studies evaluating serum CRP values in CVI.

Bouman et al.[4] measured serum CRP values in patients with PTS and showed that CRP values remained higher for a long time even after recurrences. Similarly, Krieger et al.[2] reported that serum CRP values might remain higher in the mid- and long-term following acute DVT. Increased CRP values in PTS also indicate an underlying inflammatory process. Indeed, PTS itself is a clinical entity developing on the ground of inflammation.[4] Thus, we excluded previous venous thrombosis to rule out possible effects of inflammation on serum CRP values.

Another factor that can increase serum CRP values is acute or chronic limb ulceration due to CVI or PTS. As mentioned previously, the patients with limb ulceration were excluded from our study, as an underlying inflammatory process might negatively affect our results.

Gomez et al.[5] measured tissue CRP values with enzyme-linked immunoassay method and reported that tissue CRP values of varicose, but small-diameter saphenous veins, were lower, compared to that of normal-diameter saphenous veins. The authors concluded that low tissue CRP values indicated endothelium-limited inflammation rather than extensive vessel wall inflammation. On the other hand, Sayer and Smith[12] immunohistochemically examined the tissue-level T lymphocyte, macrophage/monocyte, neutrophil, and mast cell behavior and found that varicose venous structures had a higher level of inflammation, compared to normal tissues. In our study, we evaluated circulatory CRP values and we were unable to obtain any inflammatory findings. We assumed that our findings are in consistent with findings of Gomez et al.[5] in respect to the presence of inflammatory process in varices.

In our study, there was a statistically significant difference in the WBC levels between the two groups. Additionally, there was a significant correlation between CRP and WBC levels among patients in the non-varice group, but not in the varice group. These findings indicate that patients with CVI did not have any infective event.

During the enrollment process, we excluded subjects with a history of surgery in their life span. Harris et al.[13] found that 7.5% of the patients in the intensive care units for surgery developed DVT during follow-up. Therefore, for the sake of increasing validity of the study, we excluded

these patients to prevent inclusion of any case who postoperatively developed CVI secondary to asymptomatic DVT.

Small-size cohort was one of the limitations to the study, as extreme values in such small-size studies can affect statistical analysis results. However, 95% of patients in our study population (n=95) had CRP values less than 10 mg/L. The other limitation to the study was the lack of confirmation of CRP values with other inflammation markers, except WBC. However, we enrolled our study from overall population to test the values in the real-world setting. Therefore, we attempted to test our hypothesis in the simplest way.

In conclusion, CRP is not a valuable biomarker to identify the presence of venous insufficiency in which inflammation is involved in its etiology. However, further large-scale randomized studies utilizing other biomarkers are needed to search the role of inflammation in the varice etiology are needed.

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