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The Importance of Inflammatory Markers in Predicting Chronic Venous Insufficiency

İnflamatuar Belirteçlerin Kronik Venöz Yetmezliğini Tahmin Ettirmedeki Önemi

ORIGINAL ARTICLE

ABSTRACT

Objective: Chronic venous insufficiency can be missed unless it comes to mind. We need a simplified diagnosis of chronic venous insufficiency. This study is aimed to analyze the potential role of inflammatory markers like monocyte count/high-density lipoprotein cholesterol on the diagnosis of chronic venous insufficiency.

Methods: This is a retrospective study. A total of 419 patients admitted to our clinics between September 1, 2019, and January 20, 2021, were included. Blood tests and venous Duplex ultrasound examinations applied to lower limb veins on the same day were studied. Monocyte count/high-density lipoprotein cholesterol was measured. A reflux time longer than 1 second in Duplex ultrasonography was considered venous insufficiency. The patients were divided into 2 groups according to the presence or absence of venous insufficiency. The relation between these results and the presence of venous insufficiency was examined.

Results: When compared with the patients without venous insufficiency, monocyte count was higher (0.61 ± 0.18 vs. 0.55 ± 0.15 10^9/L; $P = .00$) and high-density lipoprotein cholesterol was found to be lower (49 ± 9.1 vs. 53.4 ± 13.6 mg/dL; $P = .02$) in the patients with chronic venous insufficiency. The monocyte count to high-density lipoprotein cholesterol ratio was higher in the patients with chronic venous insufficiency (12.5 ± 5 vs. 10.9 ± 4; $P = .005$). According to multivariate regression analysis, monocyte count (95% CI: 1.003-1.035; $P = .020$) and monocyte count to high-density lipoprotein cholesterol ratio (95% CI: 1.017-1.154; $P = .013$) were independent risk factors for the occurrence of venous insufficiency.

Conclusions: If the monocyte count to high-density lipoprotein cholesterol ratio is high, it may be predicted that this patient may have chronic venous insufficiency. This prediction may focus us on the lower extremity examination in clinical routine practice.

Keywords: Chronic diseases, high-density lipoprotein (HDL) cholesterol, inflammation, monocyte count, venous insufficiency

ÖZ

Amaç: Kronik venöz yetmezlik akla gelmedikçe gözden kaçabilecek bir hastalıktır. Kronik inflamasyonun venöz kapakçıkların hasar görmesinde rol oynadığı düşünülmektedir. Bu çalışma, monosit sayısı ve yüksek yoğunluklu lipoprotein kolesterol oranı ve benzer diğer inflamatuar belirteçlerin kronik venöz yetmezlik tanısındaki potansiyel rolünü analiz etmeyi amaçlamaktadır.

Yöntem: Çalışma retrospektif olarak dizayn edildi. Çalışmaya 1 Eylül 2019 ile 20 Ocak 2021 tarihleri arasında polikliniğe başvuran toplam 419 hasta dahil edildi. Hastaların kan testleri ve aynı gün yapılmış olan alt ekstremite venöz Doppler ultrason sonuçları değerlendirildi. Doppler ultrasonografide reflü zamanının bir saniyeden uzun olması venöz yetmezlik sayıldı. Venöz yetmezlik varlığına göre hastalar iki gruba ayrıldı. Kan tetkiklerinden elde edilen inflamatuar göstergeler ile venöz yetmezlik varlığı arasındaki ilişki incelendi.

Bulgular: Kronik venöz yetmezliği olmayan hastalarla karşılaştırıldığında venöz yetmezliği olan hastalarda monosit sayısı daha yüksek (0,61 ± 0,18 ve 0,55 ± 0,15 10^9/ L; $P = ,00$) ve yüksek yoğunluklu lipoprotein kolesterol daha düşük (49 ± 9,1 ve 53,4 ± 13,6 mg/dL; $P = ,02$), monosit sayısının yüksek yoğunluklu lipoprotein kolesterole oranı daha yüksek saptandı (12,5 ± 5 ve 10,9 ± 4; $P = ,005$). Çok değişkenli regresyon analizine göre, monosit sayısı (%95 CI: 1,003-1,035; $P = ,020$) ve monosit sayısının yüksek yoğunluklu lipoprotein kolesterole oranı (%95 CI:1,017-1,154; $P = ,013$) venöz yetmezliğin ortaya çıkması için bağımsız risk faktörleriydi.

Sonuç: Monosit sayısının yüksek yoğunluklu lipoprotein kolesterole oranı yüksekse diğer kronik inflamatuar hastalıklar gibi kronik venöz yetmezliği varlığını da düşünmeliyiz. Bu öngörü günlük pratikte bizi alt ekstremite muayenesine odaklayabilir.

Anahtar Kelimeler: Kronik venöz yetmezlik, yüksek yoğunluklu kolesterol, inflamasyon, monosit sayısı, venöz yetmezlik

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Introduction

Chronic venous insufficiency (CVI) of the lower limbs is characterized by signs as a result of functional abnormalities of the veins. Symptoms include aching, swelling, cramps, itching, and burning sensations.[1] The common cause of CVI is superficial insufficiency of the venous valve.[2] Inflammation is thought to play an important role in venous valve damage. Inflammatory cell sequestration toward the venous valve is observed and monocytes play role in regulating inflammation by modulating cytokines.[3] High-density lipoprotein cholesterol (HDL-C) inhibits the expression of vascular adhesion molecules and prevents monocyte uptake into the vascular wall.[4-7] According to previous studies, monocyte/HDL-C and neutrophil/lymp hocyte were found to be predictors of mortality in patients with acute pulmonary embolism.[4] In another study, increased monocyte/HDL-C was significantly associated with retinal vein occlusion.[5] Therefore, the monocyte/HDL-C is a simple estimation method to predict inflammation and is reported as a significant predictor of cardiovascular diseases.[6,7]

As inflammation can cause damage to the venous valves, it may be considered that the monocyte/HDL-C ratio is elevated in CVI. Thus, this study is aimed to analyze the potential role of typical inflammatory markers on the diagnosis of severe CVI and pathophysiology of CVI.

Methods

Study Population

Our study included a total of 419 patients who were admitted to our clinic because of venous insufficiency between September 1, 2019, and January 20, 2021. Our study was retrospective, patient information was obtained from the hospital information management system. Blood tests performed on the same day with venous Duplex imaging were compared. The patients were divided into 2 groups as with and without venous insufficiency. Patients with CVI were named first group patients, and patients without CVI were called second group patients. Patients with hematologic severe diseases (leucocythemia and acute or chronic infection or inflammatory condition), any chronic severe disease, and pregnancy were excluded.

Laboratory Examination of the Blood

In our laboratory, all routine biochemical analyses were performed using an autoanalyzer (Roche Diagnostic Modular Systems, Tokyo, Japan). Monocyte count was defined by differential analysis of complete blood count, and the monocyte/HDL-C ratio was measured as the ratio of the monocyte $\times 10^4$ to the HDL-cholesterol. The reference value for monocyte was 0-1 $\times 10^9$/L.

Venous Duplex Imaging

Venous Duplex imaging results were examined from the hospital information system. The techniques applied in the study are Valsalva maneuver, compression, augmentation, examination of the vessel lumen with different frequencies, and application of color and power Doppler. Reflux or retrograde flow in deep, superficial, or perforating veins causing distal venous pressure was termed as CVI. In our study, only the vena saphena magna data were examined to standardize the evaluation. Color-flow Doppler scanning and spectral analysis were evaluated. Significant flow toward the feet (reflux time > 1.0 seconds) was defined as reflux. The presence of reflux was noted. Reflux time was calculated by the spectral analysis and noted.

Statistical Analysis

All statistical analyses were applied in Statistical Package for the Social Sciences version 22.0 Windows (SPSS Inc, Chicago, Ill, USA). Categorical variables were compared by use of the chi-square test and Fisher's exact test. Continuous variables (mean ± SD) were compared normally distributed variables with Student's *t*-test and non-normally distributed variables with the Wilcoxon rank-sum test. Multivariable logistic regression analyses were performed to identify the independent risk factors of CVI. A *P* value <.05 was considered statistically significant.

Ethical Considerations

Ethical committee approval was received from the Ethics Committee of Health Sciences University Sadi Konuk Education and Research Hospital (Date: June 17, 2019, Decision No: 2019-12-13).

Results

When venous Duplex ultrasound results are examined, CVI was detected in 329 (mean age: 48.7 ± 12.9 years, 65.8% female) patients and was not detected in 90 (mean age: 48.6 ± 13.6 years, 86.1% female) patients. After patients were divided into 2 groups as described, a comparison of baseline clinical and laboratory parameters between the first and second group patients was presented in Table 1.

Monocyte count was significantly higher in the first group, while lipid and other parameters were found to be similar. The monocyte/HDL-C ratio was statistically higher in the first group.

Logistic regression analysis was performed among the different parameters in the first and second group patients. The monocyte/HDL-C ratio independently determined patients with CVI (Table 2).

The correlation with reflux time was examined. The correlation of laboratory results with groups formed according to this reflux time is presented in Table 3. It was found that venous reflux time correlated only with monocyte count and monocyte/HDL-C ratio, while no significant correlation was found with the other blood values.

Discussion

In our study, we found that the monocyte/HDL-C ratio was associated with the CVI. This ratio was considered a predictor of many diseases in previous studies. We have also added that it may be a CVI predictor. To the best of our knowledge, our study is the first to find a relationship between the CVI and the monocyte/HDL-C ratio. In our study, the monocyte/HDL ratio was found to be higher as the venous reflux time increased due to the increase in the monocyte count and the limited decrease in the HDL. Venous disease of lower extremity probably causes capillary stasis and local hypoxia. Fall in the partial oxygen pressure in the standing position has been demonstrated in lower limb veins in venous disease. Previous

Table 1. Baseline Clinical and Laboratory Parameters

	First Group (*n* = 329)	Second Group (*n* = 90)	*P*
Age (year)	48.7 ± 12.9	48.6 ± 13.6	.964
Gender (male)	204 (65.8)	62 (86.1)	.01
Body mass index (kg/m^2)	26.2 ± 3.8	26.0 ± 3.6	.702
DM, n (%)	257 (82.9)	58 (80.6)	.637
HT, n (%)	215 (69.4)	55 (76.4)	.238
HL, n (%)	225 (73.6)	54 (72.6)	.860
Total cholesterol (mg/dL)	206.4 ± 38.7	209.2 ± 34.1	.161
HDL-cholesterol (mg/dL)	49 ± 9.1	53.4 ± 13.6	**.02**
LDL-cholesterol (mg/dL)	121.3 ± 33.8	125.1 ± 32.1	.810
Triglyceride (mg/dL)	150.3 ± 88.8	135.8 ± 74.2	.213
White blood cell count (10^3/mm^3)	7.7 ± 1.8	7.57 ± 1.85	.333
Neutrophil (10^9/L)	4.4 ± 1.36	4.22 ± 1.2	.145
Lymphocyte (10^9/L)	2.45 ± 0.73	2.49 ± 0.71	.643
Monocyte (×10^9/L)	0.61 ± 0.18	0.54 ± 0.14	**.00**
Platelet (×10^9/L)	248.47 ± 63.76	264.21 ± 64.57	.06
Lymphocyte ratio (%)	32.2 ± 7.6	33.3 ± 6.6	.2
Monocyte ratio (%)	8 ± 2.1	7.6 ± 1.7	.055
Neutrophil ratio (%)	56.5 ± 8.3	56 ± 7.1	.512
Red cell distribution width	14.9 ± 19.9	13.1 ± 1.5	.322
Neutrophil/lymphocyte ratio	1.94 ± 0.85	1.78 ± 0.61	.08
Platelet/lymphocyte ratio	1.09 ± 0.38	1.11 ± 0.3	.5
Monocyte/HDL-C ratio	12.5 ± 4.8	10.8 ± 4	**.001**

HDL, high-density lipoprotein; LDL, low-density lipoprotein; DM: Diabetes mellitus, HT: Hypertension, HL: Hyperlipidemia.

Bold means the significance lower than 0.05 for *P*-value

studies have demonstrated that hypoxia may affect endothelial cells activation.[7,8] The neutrophils, monocytes, activated T lymphocytes, macrophages, and mast cells accumulate in the site of inflammation.[9] In contrast to monocyte functions, HDL is an agent that has anti-inflammatory and antithrombotic properties by regulating monocyte activation.[10] High-density lipoprotein prevents the displacement of macrophages and oxidation of low-density lipoprotein and also promotes the flow of cholesterol from cells.[11] The proteins

Table 2. According to Multivariate Regression Analysis, Independent Risk Factors for the Occurrence of Venous Insufficiency

Parameters	Odds Ratio	95% CI	*P*
Monocyte/high-density lipop rotein-cholesterol ratio	1.102	1.037-1.171	**.020**

Bold means the significance lower than 0.05 for *P*-value

Table 3. Correlation of Venous Reflux Time with Laboratory Parameters

Parameters	*r*	*P*
Total cholesterol	–0.003	.949
HDL-cholesterol	–0.076	.119
LDL-cholesterol	0.026	.616
Triglyceride	0.038	.454
White blood cell count	0.045	.385
Neutrophil	0.083	.107
Lymphocyte	–0.044	0.395
Monocyte	**0.171**	**.000**
Platelet	–0.067	.189
Lymphocyte ratio	–0.089	.082
Monocyte ratio	0.093	.069
Neutrophil ratio	0.059	.248
Red cell distribution width	0.093	.069
Neutrophil/ lymphocyte ratio	0.091	.076
Platelet / lymphocyte ratio	–0.020	.693
Monocyte/HDL ratio	**0.139**	**.040**

Bold means the significance lower than 0.05 for *P*-value

found in HDL are not limited to lipid metabolism; researchers have consistently found proteins in HDL particles linked to inflammation, complement activation, and immunity. Inflammation gives rise to metabolic and structural changes in HDL. In mice, acute inflammation results in a decrease in HDL-C and an increase in circulating triglycerides.[12] In humans, inflammation leads to changes in lipid content, marked by an increase in free cholesterol and triglycerides and a decrease in phospholipids. One of the characteristic features of HDL remodeling during inflammation is a major increase in the content of the acute phase protein serum amyloid A. Studies of acute inflammation showed that in addition to overall protein and lipid content changes, nearly one-third of HDL proteome was altered by inflammation.[13] For the reasons mentioned above, it is very reasonable to use a single marker, monocyte/HDL-C ratio, as an inflammatory marker by proportioning these 2 separate markers, monocyte, and HDL-C. A growing number of studies show that the degree of venous insufficiency correlates with inflammation markers.

In our study, no significant relationship was found between the platelet (PLT)/lymphocyte (LYM) ratio, neutrophil (NEU)/LYM ratio, and the CVI. There are increasing numbers of studies showing that the PLT/LYM ratio changes in inflammation and the thrombotic process. The number of lymphocytes is expected to increase in the chronic inflammatory process. Moreover, it is expected that the number of platelets will decrease in the process of inflammation and thrombosis. In the past decade, the PLT/LYM ratio has been accepted as a universal marker in many neoplastic, inflammatory, and prothrombotic conditions.[14] In the light of all these studies, we thought

that due to an increased prothrombotic state in venous insufficiency, the PLT/LYM ratio might be correlated with the level of VI. However, in our study, no significant relationship was found between the CVI and the PLT/LYM level.[15] According to our study results, it can be said that monocyte/HDL-C is superior to NEU/LYM and PLT/LYM in the diagnosis and determining the severity of venous reflux.

Limitations

The current study had some shortcomings. This was a retrospective study, and inferences might not reflect direct causal effects between monocyte/HDL-C ratio and CVI. Sedentary lifestyle, prolonged standing, lower extremity trauma, high estrogen states, pregnancy, and smoking must be investigated. We measured the monocyte/HDL-C ratio only at baseline rather than the use of several measurements taken at different time points, so serial monocyte/HDL-C ratio variations were not evaluated. The impact of other inflammatory markers, such as C-reactive protein, has not been evaluated due to a lack of data. Finally, we did not have information about diabetes drugs that may affect inflammation parameters.

Conclusion

The monocyte/HDL-C ratio can be calculated easily from the routine blood parameters. We found that the monocyte/HDL-C ratio easily calculated by routine blood tests was associated with the CVI presence. If the monocyte/HDL-C ratio is high, it may be predicted that this patient may have CVI. This prediction may focus us on the lower extremity examination in clinical routine practice.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Health Sciences University Sadi Konuk Education and Research Hospital (Date: June 17, 2019, Decision No: 2019-12-13).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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