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Increased CRP/albumin ratio is associated with superficial venous reflux disease and varicose vein formation

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SOUHRN

Kontext: Nedávno byl publikován názor, že kromě zvýšeného žilního tlaku může vznik a progresi křečových žil ovlivňovat i zánět. Poměr C-reaktivního proteinu (CRP) a albuminu (CRP/albumin ratio, CAR) představuje nový marker zánětu spojený s nepříznivou prognózou u různých skupin pacientů. Cílem naší studie bylo zjistit vztah mezi průměrem varikózní velké safény (varicose greater saphenous vein, VSM) a parametrem CAR.
Metody: Do studie bylo zařazeno celkem 150 pacientů s nedostatečností VSM (skupina 1, n = 114) a nepostiženými VSM (n = 36). Průměr VSM se měřil B-mode ultrazvukem a reflux se kvantifikoval délkou uzavírání chlopně měřenou spektrální dopplerovskou křivkou. Krevní vzorky se odebíraly při zařazování pacientů do studie. Hodnota CAR se stanovuje vydělením hodnoty CRP hodnotou albuminu v séru.
Výsledky: Skupinu 1 tvořilo 21 (18,4 %) mužů a 93 (81,5 %) žen; ve skupině 2 bylo 7 mužů a 29 žen. Průměrný věk pacientů v obou skupinách byl podobný (48,02 ± 12,20 roku ve skupině 1 vs. 44,9 ± 8,92 roku ve skupině 2; p = 0,44). Průměrná hodnota indexu tělesné hmotnosti (BMI) pacientů se významně nelišila (skupina 1: 26,4 ± 3,7 kg/m^2 vs. skupina 2: 25,7 ± 4,2 kg/m^2; p = 0,13). Průměrné hodnoty průměru VSM byly 5,70 ± 0,29 mm ve skupině 1 a 3,21 ± 0,34 mm ve skupině 2 (p = 0,0023). Průměrné hodnoty CRP a albuminu ve skupině 1 byly 6,18 ± 4,99 mg/l, resp. 4,45 ± 0,27 g/dl; ve skupině 2 to bylo 4,25 ± 2,46 mg/l, resp. 6,18 ± 1,14 g/dl (hodnota p pro CRP = 0,049, hodnota p pro albumin = 0,074). Poměr CRP/albumin ve skupině 1 činil 1,28 ± 1,34; ve skupině 2 byla naměřena hodnota 1,11 ± 1,21, tedy statisticky nevýznamný rozdíl (p = 0,58). Byla nalezena středně těsná korelace mezi průměrem VSM a poměrem CRP/albumin i refluxem povrchových žil (r: 0,48).
Závěr: Zvýšený poměr CRP/albumin je spojen se zvýšenou incidencí varixů a větším průměrem velké safény, a tedy i vyšší incidencí refluxu povrchových žil. Zjištění podporují hypotézu, že ve vzniku křečových žil může hrát jistou úlohu systémový zánět.

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ABSTRACT

Background: It has been recently postulated that inflammation may have an effect on varicose vein development and prognosis, besides increased venous pressure. CRP/albumin (CAR) is a novel inflammatory marker associated with poor prognosis in a various group of patients. Our aim in this study was to investigate the relation between varicose greater saphenous vein (VSM) diameter and CAR.
Methods: A total of 150 patients with patients VSM insufficiency (Group 1, n: 114) and normal VSM (n: 36) were included in the study. The diameter of the VSM was measured with B-mode ultrasound, and reflux was quantified based on valve closure time using Doppler spectral tracings. Blood samples were taken during recruitment. The CAR value is determined by dividing the serum CRP level to the albumin level.
Results: There were 21 (18.4%) males and 93 (81.5%) females in Group 1 and 7 males and 29 females in Group 2. Mean age of the patients were similar in both groups (48.02±12.20 years in Group 1 vs. 44.9±8.92 years in Group 2, p = 0.44). Mean BMI of the patients did not differ significantly (Group 1: 26.4±3.7 kg/m^2

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vs. Group 2: 25.7±4.2 kg/m^2, p = 0.13). The mean diameter of VSM was measured 5.70±0.29 mm in Group 1 whereas 3.21±0.34 mm in Group 2 (p = 0.0023). Mean CRP and albumin values in Group 1 were 6.18±4.99 mg/L and 4.45±0.27 g/dL whereas 4.25±2.46 mg/L and 6.18±1.14 g/dL in Group 2, respectively (p value for CRP = 0.049, p value for albumin = 0.074). CRP/albumin was 1.28±1.34 in Group 1 and 1.11±1.21 in Group 2, which was not statistically significant (p = 0.58). There was a positive moderately strong correlation between VSM diameter and CRP/albumin ratio as well as superficial venous reflux disease (r: 0.48).
Conclusion: CRP/albumin ratio is associated with increased incidence of varicose veins and increased diameter of greater saphenous vein; hence, superficial venous reflux disease. The findings support the hypothesis that systemic inflammation may play a role in varicose vein disease.

Introduction

Varicose veins are among the most common conditions of chronic venous reflux disease (CVD).[1] Reports about the varicose vein prevalence varies between 5–30% in general population, and it deteriorates the quality of life of the patients.[1] Meanwhile, the economic burden of the disease rises, as its incidence increases.[2] Vena saphena magna (VSM) incompetence is the most widespread site of the upper-knee segment varicose disease.[1] Although venous hypertension, incompetence of venous valves, and blood reflux are well known mechanisms of venous reflux, inflammation is another potential factor suggested for pathogenesis.[3] The fundamental role of inflammation in other vascular diseases has already been recognised.[3] Moreover, inflammatory markers have been shown to be more elevated in blood taken from varicose veins than systemic circulation.[3,4]

C-reactive protein (CRP) is an acute phase reactant produced upon inflammatory situations.[5] Several studies have investigated the relation between CRP and venous function.[6,7] Albumin is also considered as an inflammatory marker, and its low levels have been associated with poor nutrition and worse outcomes in various inflammatory conditions including leg ulcer healing.[5,8] CRP to albumin ratio (CAR) is a novel inflammatory indicator, assumed to be more powerful than the each marker alone in terms of determining inflammatory status.[9] Up to now, the significance of CAR has been investigated in various clinical situations such as diabetes mellitus, coronary artery disease, cancer, and vasculitis.[9]

The literature lacks reports regarding the correlation between the diameter of the VSM, and inflammation and nutrition markers. The aim of this study was to evaluate the correlation between CAR and superficial venous reflux disease related with the varicose veins and the diameter of the VSM.

Patients and methods

The study comprised a total of 150 patients. Among them 114 consecutive patients (21 [18.4%] males, 93 [81.5%] females) comprised the study group with superficial venous reflux disease (Group 1) whereas 36 healthy individuals (7 [19.4%] males, 29 [80.5%] females) comprised the control group (Group 2). Demographic characteristics were retrospectively reviewed from the retained electronic file records of the participants. This study was conducted in accordance with the Declaration of Helsinki. The local institutional ethics committee approved the study.

The main symptoms of the patients were pain, edema, itching and cramp in the legs. Patients with active or chronic infectious disease, autoimmune disease, cerebrovascular disease, morbid obesity, peripheral arterial disease, hematological diseases, severe hepatic and renal disease, malnutrition, deep vein thrombosis, venous ulcers and malignancy were excluded from the study. Doppler ultrasonography was performed on all patients. The patients were carefully examined about venous insufficiency and increased diameter of VSM. Also, patients were evaluated by taking blood samples to examine biochemical parameters.

After 12 hours fasting, venous blood samples were obtained from antecubital veins. LDL, urea, creatinine, hemoglobin, white blood cells (WBC), CRP and albumin values were evaluated.

Greater saphenous vein diameter was measured with duplex ultrasound 3 cm below the saphenofemoral junction, while the patient was standing. Diameters were measured on B-mode transverse projections at the crossing of the fascia. An ultrasound scanner equipped with a 7.5-MHz transducer was used in all cases (ATL HDI 3000, Advanced Technology Laboratories, Bothell, Wash). The Clinical, Etiology, Anatomy, and Pathophysiology (CEAP) classification was used in the assessment of venous disease and the clinical findings were examined with the Venous Clinical Severity Score.

In the patients who had saphenofemoral junctional and/or greater saphenous vein reflux with manual compression when the patient is standing or with Valsalva maneuver for more than 0.5 second and with measured diameter of the greater saphenous vein more than 5.5 mm in Doppler ultrasonography, the interventional therapy was planned. All the patients are prescribed compression stockings.

Statistical analysis

Number Cruncher Statistical system (NCSS) (Kaysville, Utah, USA 2007) programme was used for statistical analysis. Study data were analyzed using descriptive statistical methods such as mean, standard deviation, median, frequency, ratio, minimum, maximum. Normally distributed quantitative data were analysed by Student t test, and non-normally distributed data were analysed by Mann–Whitney U test. Comparison of qualitative data was performed by Fisher Exact Test. Spearman's rank correlation was used to test the correlation among data. The r values below 0.2, between 0.2–0.4, 0.4–0.6, and 0.6–0.8 and above 0.8 indicated very weak or no correlation, poor correlation, moderate corre-

Table 1 – Demographic features of the patients in groups

Demographic features	Group 1 (n: 114)	Group 2 (n: 36)
Male	21 (18.4%)	7 (19.4%)
Female	93 (81.6)	29 (80.5%)
Mean age (years)	48.02±12.20	44.9±8.92
BMI (kg/m^2)	26.4±3.7	25.7±4.2
Smoker	52 (45.6%)	13 (36.1%)
Ex smoker	20 (17.5%)	10 (27.7%)
Deep venous insufficiency	17 (14.9%)	–
Superficial venous reflux	86 (75.4%)	–
Bilateral greater saphenous vein reflux	16 (14%)	–
Lesser saphenous vein insufficiency	12 (10.5%)	–
Perforating vein reflux	17 (14.9%)	–
Increased VSM diameter without reflux	28 (24.6%)	–
The mean diameter of VSM (mm)	5.70±0.29	3.21±0.34
Mean CRP value (mg/dL)	6.18±4.99	4.45±0.27
Mean albumin value (g/dL)	4.25±2.46	6.18±1.14
CRP/albumin (CAR) value	1.28±1.34	1.11±1.21

BMI – body mass index; CAR – CRP to albumin ratio; CRP – C-reactive protein; VSM – greater saphenous vein.

Table 2 – Correlation analysis

Correlation	r value
CRP and VSM diameter	0.52
Albumin and VSM diameter	–0.09
CAR and VSM diameter	0.48
CRP and bilateral venous reflux	0.42
Albumin and bilateral venous reflux	–0.07
CAR values and bilateral venous reflux	0.4
CRP and lesser saphenous vein reflux	0.45
Albumin and lesser saphenous vein reflux	–0.08
CAR values and lesser saphenous vein reflux	0.42
CRP and perforating veins reflux	0.41
Albumin and perforating veins reflux	–0.05
CAR values and perforating veins reflux	0.4
CRP and deep venous system reflux	0.47
Albumin and deep venous system reflux	–0.08
CAR values and deep venous system reflux	0.45

CAR – CRP to albumin ratio; CRP – C-reactive protein; VSM – greater saphenous vein.
r value:
<0.2: Very weak or no correlation
0.2–0.4: Poor correlation
0.4–0.6: Moderate correlation
0.6–0.8: Strong correlation
>0.8: Very strong correlation

lation, strong correlation and very strong correlation, respectively. The *p* values (two-tailed) lower than 0.01 with 99% confidence level and 0.05 with 95% confidence level were considered as statistically significant.

Results

The cohort consisted of a total of 150 patients divided into two groups. Patients with superficial venous reflux disease (n: 114) comprised Group 1 and healthy individuals devoid of varicosities were included into Group 2. There were 21 (18.4%) males and 93 (81.5%) females in Group 1 and 7 males and 29 females in Group 2. Mean age of the patients in Group 1 was 48.02±12.20 years and 44.9±8.92 years in Group 2, which were similar (p = 0.44). Diabetes mellitus and hypertension was not detected in any patients in both groups. Body mass indexes were calculated 26.4±3.7 kg/m^2 in Group 1 vs. 25.7±4.2 kg/m^2 in Group 2 (p = 0.13). Seventy-two patients were smokers and 20 of them were ex-smokers in Group 1 and corresponding numbers in Group 2 were 23 and 13. Demographic features of the patients in both groups are presented in Table 1.

All the patients underwent duplex USG of the symptomatic lower extremity. Doppler USG revealed deep venous insufficiency in 17 patients in Group 1 as well as superficial venous reflux disease in 102 legs. Bilateral greater saphenous vein reflux disease was detected in 16 patients. Lesser saphenous vein insufficiency and perforating vein reflux disease was present in 12 and 17 patients, respectively in Group 1. Twenty-eight patients with varicosities did not have refluxing VSM despite increased VSM diameter. The mean diameter of VSM was measured 5.70±0.29 mm in Group 1 where as 3.21±0.34 mm in Group 2 (p = 0.0023). Mean CRP and albumin values in Group 1 were 6.18±4.99 mg/dL and 4.45±0.27 mg/dL where as 4.25±2.46 g/dL and 6.18±1.14 g/dL in Group 2, respectively (p value for CRP = 0.049, p value for albumin = 0.074). CRP/albumin was 1.28±1.34 in Group 1 and 1.11±1.21 in Group 2, which was not statistically significant (p = 0.58). There was a positive moderate correlation

between the VSM diameter and CRP (r: 0.52). The correlation between albumin and VSM diameter was negative; however, very weak (r: –0.09). Again there was a positive moderately strong correlation between VSM diameter and CAR (r: 0.48).

The correlation analyses were also performed between the CRP, albumin, CAR values and venous reflux disease affecting both legs, lesser saphenous vein, perforating veins and deep venous system. Similarly, there was a positive and moderately strong correlation with CRP values, negative and very weak correlation with albumin and moderately strong positive correlation with CAR. The data regarding the correlation analysis are presented in Table 2.

Discussion

Venous insufficiency is a disease of the mankind even described in the ancient medical writings. It has a life-long prevalency approximately 30% in general population.[10] It leads to discomfort in the lower extremities, cramps, pain and in advanced cases, edema, pigmentation and ulcer formation all of which significantly affect the quality of life of the patients.[11] The sapheno-femoral junction insufficiency and/or reflux disease of the VSM are blamed for superficial venous reflux phenomenon in most instances.[12]

Various mechanisms are accused in the formation of varicose veins. Insufficient valves promoting vein dilation, venous stasis, and eventually venous hypertension are known to be the principle mechanisms.[6] Increased venous pressure and valve coaptation defects are the identifiable known factors; however, the underlying mechanisms are still controversial.[13] The cellular events are thought to be an important factor in the beginning and progression of the pathology.[14] In this context, some factors such as perivascular fibrin cuffs, ischemia, hypoxia and inflammation are proposed in the etiology. In some studies, white blood cell infiltration was detected as a supporting factor of the inflammation role in the etiology of varicose veins.[13]

The triggering mechanism of the inflammatory cascade may be the pathological environment as a result of elevated venous pressure and a change in shear stress.[13] It is thought that increased venous pressure and wall hypoxia may cause leukocyte activation and migration. This mechanism leads to mediator secretion which ends up decreased elasticity of venous wall.[15] TGF-β1 is one of the released substances following the inflammation. The overexpression of TGF-β1 was found associated with increased production of inducible nitric oxide (NO) synthase in varicose veins. Also the overproduction of NO improves the production of TGF-β1 and this may lead to progressive hypertrophy of venous wall due to cell cycle pathology.[15] This hemodynamic alterations create an inflammatory environment leading to disease progression and complications.[6] Also, in the literature, there are some studies that have shown infectious agents such as cytomegalovirus, chlamidia pneumonia, *Helicobacter pylori*, and some herpesvirus subtypes may be responsible in the triggering of vascular inflammatory cascade.[16]

CRP and serum albumin are two of the inflammation markers and widely used in clinical practice. While CRP is a positive acute phase reactant, albumin serves as a negative acute phase reactant. Decreased albumin may be related with chronic diseases, impaired endothelial functions, and may be an indicator of inflammatory status.[17] Besides measurement of these markers is a simple and inexpensive to analyze the inflammation.[6]

Recently, the CAR has been widely studied and found to be associated with infection, malignancy, inflammation, and various others as well as for the prediction of the prognosis in certain disease states.[5] Also, CAR has been recently shown to be used as a disease activity marker in patients with Takayasu arteritis, rheumatoid arthritis and Crohn's disease.[18] Akkececi et al determined 1.14 as a cut-off value of CAR for Takayasu arteritis with 96.9% sensitivity and 96.9% specificity.[18] When compared with either sole hs-CRP or albumin alone, the CAR is found superior as a predictor of prognosis in patients with acute medical pathologies. Recently, CAR is also found strongly associated with poor prognosis in patients with tumor or sepsis. The CAR is thought to have higher sensitivity due to being a combination of two different reliable markers.[19]

The role of inflammatory cascade in the etiology of venous insufficiency attracted attention in recent years. There are several studies in the literature confirming this hypothesis.[6] Saharay et al. found acute and temporary leucocyte activation by inducing venous hypertension in patients with varicose veins.[20] Another study showed marked chemokine expression in varicose veins which they believe attracts leucocytes in the area and trigger inflammatory process.[6] Poredos et al showed more elevated levels of inflammatory markers like CRP and interleukin-6 in blood samples of drawn from the varicose veins of the patients than systemic blood.[6] Mosmiller et al. compared neutrophil count and neutrophil-lymphocyte ratio in patients with mild versus severe chronic venous insufficiency, and suggested to use neutrophil-lymphocyte ratio as a severity predictor in this clinical context.[21] Karahan et al. demonstrated a relation between the severity of the chronic venous insufficiency and serum albumin levels. Moreover, fibrinogen/albumin ratio was a good predictor of disease progression with 75% sensitivity and 87.5% specificity in their study.[22] Legendre et al. revealed lower serum albumin and higher CRP levels in patients with leg ulcers compared to controls, and an association between protein deficiency and leg ulcers healing process.[8]

In our study, we observed increased CAR in patients with varicose veins. We detected significant correlation between the CAR and superficial venous reflux disease, diameter of dilated VSM and varicose veins supporting the role of inflammation in the etiology of venous insufficiency. To the best of our knowledge, this is the first prospective study to demonstrate a correlation between CAR and varicose VSM diameter.

Limitations

This study has several limitations. The relatively small sample size of patients and single-centered design are the main limitations. Since the study was performed in a single-center, the number of patients was small to achieve a subgroup analysis. Another limitation regards to the

lack of immediate postoperative and postoperative long--term blood samples and correlation analysis; however, early postoperative period is an inflammatory state and blood samples drawn at that period would not reveal reliable correlation analysis. On the other hand, we do not know how long the healing period would last in patients undergoing conventional surgical superficial venous reflux disease or in patients receiving treatment with percutaneous endovenous techniques; hence, the study also lacks long-term follow-up blood tests.

Conclusion

In conclusion, CRP/albumin ratio has been found strongly associated with varicose VSM diameter in this present preliminary study. Further multicentre based studies with larger cohors size are warranted to validate CRP/albumin ratio cut-off values to predict various prognostic criteria for the course of the superficial venous reflux disease in the affected patients.

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