

Values of fibrinogen in relation to segmental involvement of the venous system in patients with recurrent deep vein thrombosis

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ABSTRACT

Introduction: The occurrence of recurrent venous thrombosis, despite adequate therapy, is still a topic of research in the scientific world. The site of thrombosis and the involvement of anatomical segments represent a significant factor in its occurrence. **Aim:** To correlate fibrinogen values with anatomical location and extent of verified thrombus in patients with recurrent deep vein thrombosis.

Materials and methods: In the period January 2007-January 2020, 223 patients with recurrent deep vein thrombosis were analyzed. At admission fibrinogen values were taken.

Results: There was no significant difference in fibrinogen values in relation to gender ($p = 0.842$). The difference in mean fibrinogen values between proximal ($n = 171$) and distal ($n = 27 =$ veins) were not statistically significant ($p = 0.326$). There was no difference between the average values of fibrinogen in relation to the number of segments (1 to 3) ($p = 0.298$). The largest number of patients ($n = 132$) had 2 segments affected, and fibrinogen values was 4.7 g/L (3.6-7.1 g/L). Male gender had slightly higher fibrinogen values than females, but without significance ($p = 0.091$). The age of the subjects did not correlate with fibrinogen values ($p = 0.569$). Fibrinogen values according to vein anatomical localization were statistically non-significant ($p = 0.201$).

Conclusion: Fibrinogen values were not proved to be an indicator of anatomical localization and segmental involvement in patients with recurrent DVT.

Keywords: fibrinogen, venous thrombosis, prognosis.

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INTRODUCTION

Fibrinogen (factor I) is a 45 nm-long glycoprotein with a molecular weight of 340 KDa (1). It is synthesized in the liver (2). Fibrinogen is a marker of the acute inflammatory process, has a clearly defined role in the coagulation cascade, in atherogenesis, while disorders in the concentration or function of fibrinogen increase the risk of bleeding, thrombosis or infection (3). Increased fibrinogen values significantly increase the risk of venous thromboembolism (VTE) (4). Increased values are not a marker of thrombotic risk, but have an important role in the etiology of VTE (5). An increased risk of VTE associated with higher fibrin network density (necessary with thrombus stability) and with increased resistance of plasma clots to fibrinolysis (6). In the coagulation cascade, it is influenced by thrombin, which cleaves it into fibrin monomers and participates in platelet aggregation by binding to glycoprotein IIb / IIIa (7). Among the most important anticoagulants in the blood are those that remove thrombin from the blood. The strongest of these are fibrin threads that are formed in the process of coagulation and alpha-globulin antithrombin III (1,8,9). During clot forming, about 85 to 90% of the thrombin formed from prothrombin adheres to fibrin threads during their formation (1,8). This helps prevent the thrombin from spreading to the rest of the blood, thus preventing the spreading of the clot.

VTE consists of two clinical entities; deep vein thrombosis (DVT) and pulmonary embolism (PE) (the prevalence of VTE in the general population is 1-2%) (10,11,12). The incidence of DVT is 1 per 1000 annually in adult populations (10). The disease occurs depending on age, ranging from 0.03% in persons under 50 years of age, to 0.4% in persons over 50 years

of age (10,11). Most studies show an equal prevalence of the disease in both sexes (although data from some studies suggest that it is more common in males over 50 years of age) (11,12). Available data show that more than 95% of pulmonary emboli are caused by thrombi located in deep veins of the lower extremities. (11) Larger leg veins (popliteal vein and veins above it) are a much more common source of pulmonary emboli, which are of clinical interest, and PE should be considered the most serious complication of DVT (13). Venous thrombus consists of two components, internal platelet-rich part (white thrombus) that formed Zahn lines that are surrounded by red cell dense fibrin clot (14). Fibrin, deoxyribonucleic acid and histone proteins form the outer scaffold, which is very important for the success of thrombolysis (13,14). The occurrence of recurrent venous thrombosis, despite adequate therapy, is still a topic of study in the scientific world. The site of thrombosis and the involvement of anatomical segments represent a significant factor in its occurrence (15,16,17,18). Prevention of PE is imperative. Annual incidence rate for PE ranges from 39-115 per 100,000 people, while for DVT, the incidence ranges from 53-162 per 100,000 people (16). In the six most developed European countries with a total population of 454.4 million, more than 370,000 deaths were associated with VTE (16). Anatomically proximal DVT is localized in popliteal, femoral or iliac veins, while isolated distal is localized below the knee (16).

The aim of this study was to correlate fibrinogen values with anatomical location and extent of verified thrombus in patients with recurrent deep vein thrombosis.

MATERIALS AND METHODS

In the period January 2007-January 2020, a total of 8024 patients were hospitalized at the Department of Angiology, Clinic for Heart, Blood Vessel and Rheumatic Diseases, Clinical Center University of Sarajevo, of which 1502 were diagnosed with DVT and 239 patients with recurrent DVT. Criteria for inclusion in the research: previously verified DVT, newly confirmed thrombosis and consent to participate in the study. DVT were confirmed by ultrasound VIVID S5 with 12 L linear probe (General Electric, Boston, Massachusetts, United States) or Logiq Book XP with 8L curvilinear probe (General Electric, Boston, Massachusetts, United States), Fibrinogen reference ranges are 1.8-3.8 g/L. The SPSS Windows software package (version 21.0, SPSS Inc., Chicago, Illinois, USA) and Microsoft Excel (version 11 of Microsoft Corporation, Redmond, WA, USA) were used for statistical analysis of the obtained data. In a sample of 223 patients, fibrinogen values were not distributed according to normal

distribution ($p=0.0001$). Comparison of the variables was done using nonparametric tests (Mann-Whitney U test, Kruskal Wallis) and results were presented using median and interquartile range (Q1-Q3). The relationship between fibrinogen and age was checked using Spearman's rho test. The research was conducted in accordance with the basic principles of the Declaration of Helsinki (last revision in 2013) on the rights of patients involved in biomedical research. During the realization of this research identity and all personal data of patients are permanently protected in accordance to regulations of protection of identification data. Identification number was assigned to each patient in order to protect personal information and that number was used in statistical analysis. Informed consent was obtained from all individual participants included in the study. Ethical approval was obtained from the Ethical Committee Clinical Center University of Sarajevo.

RESULTS

The research was conducted on 223 patients, 110 (49.3%) men and 113 (50.7%) women with diagnosis of recurrent DVT. The mean age of the patients was 59.58 ± 15.6 years, the youngest was 22, and the oldest was 87 years old. There was no significant difference in fibrinogen values relation to gender ($p = 0.842$).

Patients were divided according to vein segmental involvement (Table 1). The differences in mean fibrinogen values between proximal ($n = 171$) and distal ($n = 27$) part were not statistically significant ($p = 0.326$) (Table 1).

There was no difference between the average values of fibrinogen in relation to the number of segments (1 to 3) ($p = 0.298$.) (Table 2).

Table 1. Fibrinogen values related to the vein segments of the lower extremity (fibrinogen values in g/L)

	N	Min	Max	25th Perc	Median	75th Perc
upper part of lower extremities	171	0.6	27.6	3.59	4.90	7.40
distal part of lower extremities	27	2.3	24.7	3.90	4.60	9.00

Table 2. Values of fibrinogen in relation to the number of affected segments (fibrinogen values in g/L)

Number of affected segments	N	Min	Max	25th Perc	Median	75th Perc
1	21	2.9	24.7	3.70	5.50	14.05
2	132	0.6	27.6	3.60	4.70	7.10
3	45	1.1	25.6	3.50	5.10	6.30

The largest number of patients (n = 132) had 2 segments affected, and fibrinogen values was 4.7 g/L (3.6-7.1 g/L).

In 45 patients with affected 3 segments mean fibrinogen values were 5.1 g/L (3.5-6.3 g/L).

One affected segment was present in 21 patients, where mean fibrinogen value was 5.5 g/L (3.7-14.0 g / L).

Male gender had slightly higher fibrinogen values than females, but without significance (p = 0.091). The age of the subjects did not correlate with fibrinogen values (p=0.569).

Fibrinogen values according to vein anatomical localization were statistically non-significant (p = 0.201) (Table 3).

DISCUSSION

Anticoagulant therapy is indicated for all proximal DVT regardless of the symptomatology, while anticoagulation is also a treatment for distal DVT (16).

Recurrent DVT is treated with low molecular weight heparin (LMWH) if patient has not been on any anticoagulant therapy before new DVT (recurrent). If patient developed recurrent DVT while he was treated with oral anticoagulant (antagonist of vitamin K or new oral anticoagulants) or LMWH, golden standard in treatment is LMWH or unfractionated heparin (UFH) during ten days (with renal function, platelet and activated partial thromboplastin time monitoring) (16). After ten days they should be switched to LMWH or oral anticoagulant (again depends on patient characteristics) (16). Recurrence of DVT is a major clinical problem in practice. The risk for recurrent DVT is highest during the first six months after the in-

cident (19). Labropoulos et al. followed 53 consecutive patients with an acute first episode of DVT over a five-year period, and concluded that the incidence of recurrence at 5 years was 26.1% (20). Unprovoked DVT and age > 65 years were main risk factor for recurrent DVT (20). Hanson et al. followed 738 consecutive patients with symptomatic DVT for 3.7 to 8.8 years, and concluded that the 5-year cumulative incidence of recurrent venous thromboembolic events was 21.5 (21). Proximal DVT was risk factor for recurrence (21). Farzamia et al. found in 385 patients that recurrent DVT were related to blood disorders and immobility (22). Wuillemin et al. in 107 patients, 46 of whom were diagnosed with DVT, demonstrated that there was no significant difference between patients who had and did not have DVT in fibrinogen values (23). Patients DVT were divided into two groups, one with proximal and distal DVT, and there was also no significant value in fibrinogen values (23).

Klovaite et al. analyzed the Danish general population, of whom 1,679 were diagnosed with DVT alone, 1,119 with any PE, and 272 with both PE and DVT, and concluded that elevated fibrinogen was associated with an increased risk of PE in patients with DVT, but that fibrinogen values cannot be associated with the formation of PE or DVT (24).

Elevated fibrinogen values and particular anatomical localization do not play a role in thrombus prevalence in patients with recurrent DVT. However, it should be emphasized that fibrinogen is very important for fibrin network structure, and as such plays a role in thrombus structure and stability (25).

In our research, the values of fibrinogen were higher than 3.8 g/L in both proximal and distal recurrent DVT. Our research has shown that fibrinogen values

Table 3. Fibrinogen values in relation to anatomical localization (fibrinogen values in g/L)

Veins	Number	Min	Max	25th percentile	Median	75th percentile
iliac	1	16.1	16.1	.	.	.
iliac - femoral	54	.6	26.1	3.47	4.70	7.53
iliac-femoral-popliteal	47	1.1	25.6	3.30	5.00	5.80
femoral	8	3.7	16.8	3.70	4.30	5.35
femoral - popliteal	55	2.0	27.6	3.70	4.50	6.70
popliteal	15	2.9	14.9	3.90	8.10	10.70
crural	10	3.0	24.7	4.05	6.80	19.32
fibular	1	4.2	4.2	.	.	.
tibial	4	2.3	4.5	2.62	3.75	4.35
gastrocnemius	1	11.8	11.8	.	.	.
subclavia	1	5.5	5.5	.	.	.
brachial	1	7.6	7.6	.	.	.

were not significantly correlated with patient age, gender, segmental distribution, anatomical localization as well as body side in patients with recurrent DVT.

This indicates that fibrinogen values, as isolated, should not be a marker for predicting recurrence. It presents one of the markers that could be used in diagnosing DVT, and D-dimer and ultrasound should be preferred in everyday clinical practice. Individual approach to the patient, his therapy and treatment of comorbidities should be imperative, with clear stratification of patients in relation to the risk of DVT recurrence, due to more careful monitoring as well as probably longer-term anticoagulant therapy. The use of the Vienna prediction model, the Disabilities of the Arm, Shoulder and Hand (DASH) Score and the HERDOO-2 score should be a tool in the hands of physicians working with patients with DVT (26,27,28).

CONCLUSION

Fibrinogen values were not proved to be an indicator of anatomical localization and segmental involvement in patients with recurrent DVT.

DECLARATION OF PATIENT CONSENT:

The authors certify that they have obtained all appropriate patient consent forms

DECLARATION OF INTEREST

Authors declare no conflicts of interest.

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