Influence of obesity and aging on the development of superficial vein thrombosis in patients with primary varicose veins

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Abstract:

Introduction: Previous studies have demonstrated the relationship of various factors on etiology of superficial vein thrombosis (SVT), although the association of obesity and aging as independents risk factors for the development of SVT in patients with varicose veins (VVs) remains unknown. The aim of this study was to investigate the role of obesity and aging as risk factors for SVT in patients with primary VVs.

Material and Methods: Retrospective analysis was conducted of prospectively collected data from 230 outpatients with primary VVs. Demographic data, comorbidities and body mass index (BMI) were analyzed. According to medical history, clinical examination and duplex ultrasound (DUS), patients were divided in 2 groups: patients with SVT and VVs, and the control group with VVs but without thrombosis.

Results: 128 patients with a recent documented episode of SVT (85 women, mean age 56.16, SD 13.76) (SVT group) and 102 without any thrombotic event (control group) (75 women, mean age 48.67, SD 12.55) were included. Mean BMI was 27.18kg/m^2 (SD 4.7) in the SVT group and 25.36kg/m^2 (SD 3.6) in control group. Compared to those with a normal BMI (<25kg/m^2), the overweight (25kg/m^2>BMI<30kg/m^2) and obese patients (BMI>30kg/m^2) had an increased risk of SVT by 1.8 - fold (OR 1.85, p=0.038, 95% CI: 1.03-3.32) and 3.3-fold (OR 3.33, p=0.002, 95% CI: 1.53-7.22), respectively. Dislipidemia was associated with a higher risk of SVT (37% vs.18%) (OR 2.3, 95% CI 1.26-4.42). Also, patients > 60yrs showed an increased risk of SVT development by 3.5 fold compared to younger patients. In multiple logistic regression analysis the SVT risk increased by 3.7% (OR 1.037, p=0.001, 95% CI 1.04-1.06) for each year of aging and by 3.5 fold for obese patients (OR 3.5, p=0.003, 95% CI 1.53-8.05).

Conclusions: Obesity and aging appear to increase the risk of SVT development among patients with primary VVs without any other known risk factor.

INTRODUCTION

The prevalence of varicose veins (VVs) in the general population ranges between 20- 60%.[1] Superficial vein thrombosis (SVT) of the lower limbs is a common disease reported to affect 3-11% of the general population. In patients with VVs, the prevalence of SVT ranges from 4- 59%[2,3], although in many cases remains unrecognized and thus their incidence is under reported. Usually SVT is located in the great saphenous vein (GSV) at a rate of 60-80%, while in the small saphenous vein (SSV) occurs more rarely (10-20%).[4] SVT is usually more commonly detected in varicose tributaries than in main GSV trunk. Clinically, it is presented as a sensitive hard cord, circumscribed by a red zone in an area with preexisting varices.[2] Venous thromboembolism (VTE) is a complex disease involving interactions between acquired or inherited predispositions to thrombosis and various risk factors.Recent studies have demonstrated that obesity increases the risk of VTE. [6,7] However it is unclear whether obesity increases risk of SVT in patients with VVs. Another risk factor of VTE is increase in age.[8] Thus, the older the patients, the fewer risk factors are needed for the development of VTE.[9] Currently, the association of obesity and age with SVT in patients with VVs has not been adequately studied. The objective of this study was to evaluate the role of obesity and aging as risk factors for SVT in patients with primary VVs.

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MATERIALS AND METHODS

Study Design

A retrospective analysis of prospectively collected data of outpatients with an acute or recent episode of SVT and primary VVs referred to our tertiary center between April 2016 and March 2018 was performed. Also patients referred to our department during the same period with VVs without a history

of previous SVT were included as control group. Patients with previous episodes of deep vein thrombosis (DVT) or pulmonary embolism (PE), autoimmune disease, malignancy, hepatic or renal insufficiency, recent surgery or trauma, prolonged immobilization, pregnancy, sepsis, use of medications that promotes thrombosis such an oral contraceptives or hormone replacement therapy and patients receiving antithrombotic agents for any other cause such as atrial fibrillation or antiplatelet therapy were excluded.Demographic data, medical history and clinical characteristics were recorded in databases. The data obtained from each patient included gender, age, body mass index (BMI), the presence of other diseases such as hypertension, diabetes mellitus, dislipidemia, history of smoking. Dislipidemia was defined from the presence of serum total cholesterol>200 mg%, LDL>130 mg%, and/or triglycerides>150 mg%. All patients were subjected to renal and hepatic function control, and the levels of blood lipids were measured after 16 hours of fasting.

According to medical history, clinical examination and duplex ultrasound (DUS), patients were divided in 2 groups: patients with SVT and VVs, and the control group with VVs but without thrombosis (SVT or DVT).

Only outpatients with VVs that provided their consent to participate to the study and fulfilled our inclusion criteria were included

Duplex Ultrasound of the Veins

All patients underwent duplex ultrasound examination (DUS) of the superficial and deep veins of the lower limbs. DUS was used to diagnose SVT, to estimate the extent of the thrombus to exclude the presence of deep vein thrombosis (DVT). SVT was diagnosed when superficial veins were not compressible under the probe. DUS were performed by the same vascular surgeon with special interests in duplex scanning.

Body Mass Index

According to the World Health Organization (WHO), definition of obesity is through the BMI. Body mass index was calculated by dividing weight in kilograms by the square of the height in meters (Weight (Kg) / Height (m^2)). Patients were categorized in 3 subgroups: Patients with normal weight (18.5< BMI<24.9 Kg/m^2), overweight (25<BMI<29.9 Kg/m^2) and obese (BMI>30 Kg/m^2).

Statistical analysis

Statistical analysis was carried out with the use of SPSS version 21.0 for Windows, SPSS Inc, Chicago, IL. Chi square tests were applied to initially assess categorical variables. The odds ratios were estimated with confidence intervals (CI 95%). Statistically significant risk factors at p<0.20 were used in a logistic regression model. Interactions of all statistically significant factors at p<0.10 were then examined. All factors entered in the final model had an observed significance level at <0.05.

RESULTS

The study population consisted of 128 patients in the SVT group (43 men, age 56 ± 13) and of 102 patients in the control group (27 men, age 48 ± 12).The GSV was involved in 61 (47%) of the patients,SSV in 1 (0.7%) and varicose tributaries in 66 (52%).

Table 1 shows the main characteristics of the study population. Patients in the SVT group were older than controls (p=0.001). Patients older than 60 years showed an increased risk of SVT by 3.5-fold compared to younger (odds ratio 3.56, p<0.001, 95% CI: 1.90 – 6.68). Mean BMI was 27.18kg/m^2 (SD 4.7) in the SVT group and 25.36kg/m^2 (SD 3.6) in control group. More patients in the SVT group were overweight and obese (Fig1). Compared to those with a normal BMI (<25kg/m^2), the overweight (25kg/m^2>BMI<30kg/m^2) and obese patients (BMI>30kg/m^2) had an increased risk of SVT by 1.8 - fold (OR 1.85, p=0.038, 95% CI: 1.03-3.32) and 3.3-fold (OR 3.33, p=0.002, 95% CI: 1.53-7.22), respectively. Dislipidemia was also associated with a higher risk of SVT (37% vs.18%) (OR 2.3, 95% CI 1.26-4.42).

In multiple logistic regression analysis the SVT incidence increased by 3.7% (OR 1.037, p=0.001, 95% CI 1.04-1.06) for each year of aging and by 3.5 fold for obese patients (OR 3.5, p=0.003, 95% CI 1.53-8.05).

	Diseased Group n (%)	Control group n (%)	p value	Odds Ratio	95% CI
No	128	102			
Gender (Female %)	85 (73.5%)	75 (66.4%)	0.243		
Age(Mean, SD)	48 (12)	56 (13)	0.001		
Age> 60 y	63 (49%)	26 (25%)	<0.001	3.5	1.90-6.68
BMI (Mean, SD)	25 (3.6)	27 (4.7)	0.001		
BMI <24.9 Kg/m^2	44 (34%)	55 (54%)	0.458		
25<BMI<29.9 Kg/m^2	52 (41%)	35 (34%)	0.038	1.85	1.03-3.32
BMI>30 Kg/m^2	32 (25%)	12 (12%)	0.002	3.3	1.53-7.22
Dislipidemia	43 (37%)	18 (18%)	0.054	2.3	1.26-4.42
Smoking	45 (35%)	33(32%)	0.743		
Hypertension	32(26%)	25(24%)	0.598		
Diabetes melitus	23 (20%)	16(16%)	0.672		

Table 1. Main characteristics of the study population

DISCUSION

The main objective of our study was to investigate the role of obesity and aging in patients with primary VVs complicated with SVT without any other known thrombotic risk factor. Our data showed that obesity and aging are associated with an increased risk of SVT development in patients with primary VVs.

The incidence of venous thrombosis rises from 0.001% in childhood to nearly 1% in aged subjects.[8] As described in POST (Prospective Observational Superficial Thrombophlebitis) study the mean age of developing SVT is 60 years and it is generally accepted that people younger than 40 years with a venous thrombotic episode are likely to have a thrombophilia defect.[3]

In most of the studies the mean age of the patients presenting with SVT was lower than in our study. [8,10,11] This may be due the fact that these studies also included patients without VVs, with a previous episode of DVT and/or PE and other risk factors that promotes thrombosis. Moreover in some cases SVT may occur with mild or asymptomatic clinical symptoms and patients may not present for medical attention.

The risk of thrombosis increases with age. [3,12] This may be explained by a combination of factors such as reduced activity, decreased muscle tone, increased morbidity and damaged vein system. Aging causes an increase in fibrinogen, and this leads to formation of thrombin, increase of plasma viscosity and platelet aggregation.[13] Concentration of FVII, IX and others coagulations proteins is increasing without a proportional increase of anticoagulants factors. [13] Interleukin1 (IL-1) and C- reactiven protein (CPR) are increased, suggesting an inflammatory condition, which is important factor in the development of thrombus, particularly in elderly. [23] Furthermore enhanced platelet activity and increase plasminogen activate inhibitor (PAI-1) factor impairs fibrinolytic activity. [13] All the above conclude that the older the patient the fewer risk factors are needed for the development of thrombosis. [3,12]

In recent years, the prevalence of obesity has increased in the western world to a concerning level. At least 250 million people or 7% of the existing population are obese. The number of overweight patients is 2-fold or 3- fold higher. Two –thirds of all men and half of all women in Great Britain are either overweight or obese.[14] In the last decade obesity was more than doubled, with an estimated prevalence of almost 30% of the general population.[15] According to Eurostat data, the prevalence of obesity in Greece is among the highest in the Western Europe. In men above 15 y.o is 26%, and in women 18,2%, which represents the highest and second highest percentage respectively.

Severe obesity is an independent risk factor for the development of VTE, especially when the weight exceeds 175% of the ideal one.[26] Predisposes to venous stasis and is associated with many haemostatic disorders. Obesity enhances thrombosis by increasing prothrombotic factors and impairing fibrinolytic activity.[17,18] Furthermore, obesity is considered as a chronic inflammatory condition that promotes thrombosis, either by increasing IL-1, TNFa and CRP, neither by causing oxidative stress.[18] Several studies have described the association of SVT with obesity.[3,19,20] In our study the overall risk of developing SVT was higher in obese patients, compare to those with normal. The association remained fairly strong after adjustment for age.

Although we recognized obesity as a risk factor of thrombosis in patients with VVs, the presence of a significant number of obese patients may have influenced our results. Over half of our patients were overweight and 25% in the diseased group were morbidly obese. Mobilization of elderly and overweight patients is difficult and this has an obvious influence on their ability to clear thrombus. Obesity also predisposes to postthrombotic syndrome and vein ulcers.[21]

Dislipidemia was also found as a risk factor for SVT. In a recent study, dislipidemia was associated with an increased risk of recurrence of SVT.[22] However, whether obesity on its own or the associated dislipidemia is the triggering factor remains to be clarified. The high levels of nonesterified fatty acids released in obesity increase the hepatic synthesis of triglycerides and very low-density lipoprotein (VLDL), leading to lipid disorder.[23] Lipid disordes are also accompanied by platelet activation and hypercoagulabity with increased factor VII.[24] A possible limitation of our study is that we did not consider the severity of venous disease according to CEAP (Clinical, Etiological, Anatomical, Pathophysiological) classification. Patients with different varicose status were included. Another limitation is that we have not examined the existence / absence of various symptoms in our patients. Also we did not check our patients for insulin resistance, a factor that is associated with a thrombotic predisposition.

CONCLUSIONS

Our study demonstrates that obesity and aging were associated with an increased risk of SVT development among patients with primary VVs without any other known thrombotic risk factors. Larger epidemiological studies are needed to confirm the findings of our study.

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