Original Research

Association between obesity and venous thromboembolism

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Abstract

Background and aims. Obesity is associated with numerous pathological conditions, including venous thromboembolism (VTE). VTE is a multifactorial disease; more than half of the hospitalized patients are at risk for VTE.

We aimed to assess the risk of VTE associated with obesity, taking into account the class of obesity (according to the body mass index), gender, age and the intervention of other acquired risk factors.

Methods. A case-control study including 732 patients was designed. Collected data included: age, gender, body mass index, pregnancy/postpartum state, use of hormonal therapy, personal and family history of VTE, smoking, prolonged immobilization and the presence of comorbidities - acquired risk factors for VTE. The risk of VTE was expressed as odds ratio (OR) with 95% confidence interval. Multiple logistic regression analysis was used to detect the independent risk factors. P value <0.05 was considered significant statistic.

Results. Obesity was associated with a 6.2-fold increased risk for VTE. The risk of VTE associated with obesity was highest in patients aged >50 years and in cases included in classes II and III of obesity. The interaction between obesity and another acquired risk factor has almost doubled the risk of VTE. Multivariate logistic regression analysis showed obesity as an independent risk factor for VTE for both female and male patients.

Conclusions. Obesity is an independent and moderate risk factor for VTE. The risk increases with body mass index, age and the presence of other acquired risk factors.

Keywords: obesity, deep vein thrombosis, venous thromboembolism

Background and aims

Obesity, a global public health issue, is associated with numerous disorders, such as type 2 diabetes mellitus, obstructive sleep apnea syndrome, gastrointestinal disorders, depression, malignancies, stroke and cardiovascular diseases including coronary artery disease, hypertension, and venous thromboembolism (VTE). The World Health Organization (WHO) reports show that the worldwide obesity nearly tripled since 1975; in 2016, 39% of adults were overweight and 13% were obese [1]. According to WHO criteria, obesity, defined by a body mass index (BMI) of at least 30 kg/m^2, can be classified into three categories: class I low-risk obesity with a BMI of 30-34.9 kg/m^2, class II moderate-risk obesity with a BMI of 35-39.9 kg/m^2 and class III high-risk obesity, or morbid obesity, with a BMI ≥40 kg/m^2. Recent data suggest that other adiposity measures, alone or in combination with BMI, may be taken into practical consideration, especially for the assessment of the cardiovascular risk: waist circumference, waist-to-hip ratio, body fat percentage using magnetic resonance imaging or dual-energy X-ray absorptiometry [2,3].

VTE, the third most common cardiovascular disease with an overall average age- and sex-adjusted annual incidence of 117 per 100,000, comprises deep venous thrombosis (DVT) and pulmonary embolism (PE), which is the major complication of DVT [4]. VTE is a multifactorial disease, result of the

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interaction between genetic and acquired risk factors. Acquired risk factors include numerous conditions such as: increasing age, malignancy, prolonged immobility, stroke or paralysis, recent surgery, previous VTE, congestive heart failure, acute infection, pregnancy or puerperium, dehydration, hormone therapy, varicose veins, acute inflammatory bowel diseases, various rheumatologic diseases, obesity and nephrotic syndrome [4]. Multicenter studies have shown that more than half of the patients hospitalized for all reasons are at risk for VTE and the risk is higher in surgical patients (>60%) [5].

Obesity is associated with inactivity, raised intra-abdominal pressure, a chronic low-grade inflammatory state, impaired fibrinolysis, high levels of fibrinogen, von Willebrand factor and factor VIII, leading to a prothrombotic condition and elevated risk of VTE [6,7]. It has been shown that the risk of VTE increases with increasing BMI [6].The risk is higher when obesity interacts with other thrombotic risk factors.

We aimed to assess the risk of VTE associated with obesity taking into account the class of obesity, gender, age and the intervention of other acquired risk factors.

Methods

A 3-year retrospective observational case-control study including a group of 382 patients diagnosed with VTE, consecutively hospitalized in an Internal Medicine and Surgery Department of a teaching hospital in Cluj-Napoca, Romania, and a group of 350 age- and sex-matched controls without VTE, has been designed. Data have been collected from the hospital records. The inclusion criterion in VTE group was definite main or secondary diagnosis of VTE at the admission or during hospitalization; the exclusion criteria were the followings: probable VTE, clinical supposition of VTE, incomplete data. The following data were collected from all the participants: age, sex, BMI, manifestation of VTE (DVT, PE), current physiologic data (pregnancy/postpartum) use of oral contraception or hormone replacement therapy, history of previous VTE, family history of VTE, smoking, prolonged immobilization (including cast immobilization, bed rest for more than 3 days, recent long-distance travel) and the presence of comorbidities- risk factors for VTE: varicose veins, chronic obstructive pulmonary disease (COPD), congestive heart failure, stroke, acute infection, nephrotic syndrome, inflammatory bowel disease, rheumatologic disease/vasculitis (Behcet's disease, trombangitiis obliterans, antiphospholipid syndrome) malignancy, recent surgery, trauma, central venous line, dehydration, hematological diseases (polycythemia, sicklemia). The study was approved by the Ethics Committee of the University.

SPSS 15.0 for Windows (Statistical Package for the Social Sciences) was used for the data analysis. The risk of VTE associated with obesity, expressed as Odds ratio (OR) with the associated 95% confidence interval (CI), was assessed using chi-square test. Multiple logistic regression analysis was used to detect the independent risk factors. P value < 0.05 was considered significant statistic.

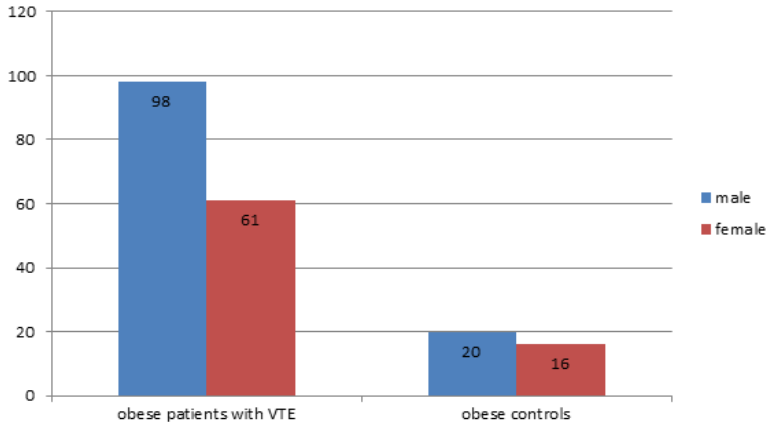
Results

The mean age was 58.6 years old in patients with VTE and 59.5 years old in controls; 63.87% of patients with VTE were male. VTE was found in 82.98% patients aged >50 years (29.58% women and 53.4% men) and in 17.02% patients <50 years old (6.54% women and 10.47% men). The absolute frequency of the risk factors in VTE group and controls and the significance of the association with VTE are shown in table I.

Table I. The assessment of the risk factors in VTE group and controls.

Risk factor	Female with VTE		Male with VTE		Controls (n=)	Association with VTE: p
	Age < 50 (n=)	Age ≥50 (n=)	Age <50 (n=)	Age ≥50 (n=)		
Obesity (BMI ≥30kg/m^2)	13	48	13	85	36	0.0001
Pregnancy/postpartum	9	0	0	0	8	0.635
Hormonal therapy	5	2	0	0	19	0.073
Personal history of VTE	4	2	13	38	14	0.0001
Family history of VTE	13	45	2	10	66	0.172
Smoking	8	16	27	75	47	0.001
Prolonged immobilization	9	17	7	95	43	0.0001
Varicose veins	12	39	8	64	30	0.001
COPD	4	13	4	64	42	0.001
Congestive heart failure	6	28	7	63	41	0.001
Stroke	0	4	1	13	6	0.023
Acute infection	0	3	2	10	27	0.068
Nephrotic syndrome	0	1	0	2	4	0.620
Inflammatory bowel disease	2	1	2	0	3	0.454
Rheumatologic disease/ vasculitis	4	0	8	1	8	0.366
Malignancy	1	17	3	24	24	0.023
Recent surgery	2	9	5	33	27	0.022

Legend: n= number of the cases (absolute frequency), BMI= body mass index, COPD= chronic obstructive pulmonary disease.

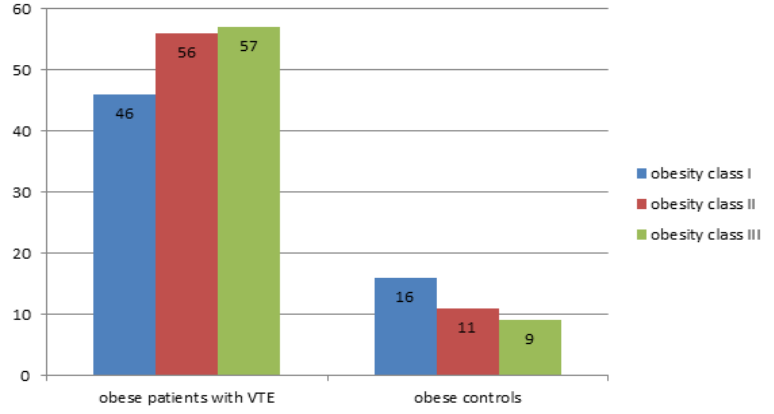


Legend: VTE = venous thromboembolism

Figure 1. The distribution of obesity amongst VTE patients and controls according to the gender.

Table II. The risk of VTE in obese patients according to gender and age.

Obesity	p	OR	95% CI (lower-upper limit)
female	0.0001	3.966	2.240-7.024
male	0.0001	5.693	3.431-9.447
age >50 years old	0.0001	6.142	3.956-9.535
age <50 years old	0.002	3.122	1.394-6.991



Legend: VTE = venous thromboembolism

Figure 2. The distribution of the classes of obesity in VTE group and controls.

The frequency of trauma, central venous line, dehydration and hematological disorders was very small for each condition in part and no further analysis regarding the association with VTE has been performed. No apparent risk factor has been identified in 9.69% of the patients.

VTE was manifested as DVT in the main majority of the cases; PE was diagnosed in 11.78% of patients.

Obesity was found in 159 patients with VTE (41.62%) of whom 61.6% were men and 83.64% were aged more than 50 years and in 36 controls, as shown in figure 1.

Obesity was significantly associated with VTE: p=0.0001, OR=6.219, 95% CI: 4.167-9.281. The association was also significant for cases complicated with PE: p=0.005, OR=3.368, 95% CI: 1.404-8.079.

Both female and male patients with obesity presented a significant elevated thrombotic risk. The risk of VTE was almost double in obese patients aged >50 years than in those younger than 50 years old, as shown in table II.

The majority of obese patients with VTE were included in classes II and III of obesity (71.07%) and presented a higher risk of VTE compared to those in class I of obesity, as shown in figure 2 and table III.

Table III. The risk of VTE according to the classes of obesity.

Class of obesity	p	OR	95% CI (lower-upper limit)
I	0.0004	2.857	1.519-4.566
II	0.0001	5.293	2.725-10.284
III	0.0001	6.645	3.236-13.641

Table IV. Multivariate logistic regression analysis.

Factor		P	OR	95% CI lower-upper limit
Obesity	female	0.0001	6.113	3.044-12.277
	male	0.0001	3.510	1.906-6.463
History of VTE	female	0.052	1.936	0.995-3.767
	male	0.0001	4.828	2.077-11.223
Smoking	female	0.407	0.379	0.308-3.757
	male	0.833	1.113	0.411-3.010
Prolonged immobilization	female	0.425	2.499	0.263-23.764
	male	0.190	3.401	0.632-20.620
Varicose veins	female	0.001	3.558	1.738-7.284
	male	0.001	4.166	1.995-8.701
COPD	female	0.160	1.972	0.764-5.087
	male	0.004	2.317	1.316-4.080
Congestive heart failure	female	0.281	1.557	0.696-3.481
	male	0.001	3.460	1.932-6.197
Stroke	female	0.752	1.351	0.209-8.711
	male	0.425	1.910	0.389-9.380
Malignancy	female	0.001	13.666	3.689-50.622
	male	0.300	1.657	0.927-1.454
Recent surgery	female	0.153	0.494	0.188-1.298
	male	0.840	1.103	0.428-2.843
Age>50 years	female	0.052	1.936	0.995-3.767
	male	0.014	1.427	1.217-2.843

History of previous episode of VTE, smoking, prolonged immobilization, COPD, heart failure, stroke, varicose veins, malignancy and recent surgery were also significant risk factors for VTE ($p<0.05$, as shown in table I). Obesity interacted with at least one of these factors in 57.86% of cases leading to a higher risk of VTE than in cases when acting alone: OR=5.619, 95% CI: 3.194-9.884 *versus* OR=2.923, 95% CI: 1.753-4.873.

Multivariate logistic regression analysis identified obesity as an independent risk factor for VTE for both women and men (p=0.0001; OR=6.113, respective OR=3.51) as shown in table IV.

Discussion

Moderate risk factors are generally associated with OR of 2-9. Obesity appears to be a moderate risk factor for VTE leading to two- to five-fold increased risk of developing VTE, compared to those with normal BMI [2,5,7,8]. Although it has been suggested that waist circumference measurement may identify better the obese patients at risk for VTE, the thrombotic risk is elevated in obese individuals no matter the method used for the assessment of obesity: body weight, BMI, waist circumference, waist to hip ratio and total body fat mass [9,10]. We used BMI for the diagnosis of obesity according to WHO criteria.

The risk increases with increasing BMI: individuals with a BMI ≥35 kg/m^2 may present a six-fold greater risk than those with normal BMI [2]. A strong, independent and linear association was found between increasing BMI and risk of PE in a large cohort of female nurses; the risk increased even with modest increases in BMI [11]. Recently it has been shown that obesity may be causally associated with VTE and the risk of DVT is up to five-fold increased [12]. Our data show a slightly higher OR (6.2) explained by the fact that more than 70% of the obese patients with VTE were included in classes II and III of obesity which are associated with a higher thrombotic risk compared to class I of obesity (OR: 6.645, 5.293 respective 2.857). However, a retrospective study including overweight and obese hospitalized patients found no increase of VTE incidence with the increasing severity of obesity, possibly explained by the enrolment of patients who received

thromboprophylaxis, which is different from our inclusion criteria [13].

Obesity is associated with DVT as well as with PE, similar with our findings [2,11,12]. A recent study using a large inpatient database found an increased prevalence of PE in obese subjects; the risk of PE was more than double compared to the control population [14]. Our findings show a slightly higher OR for PE (3.3) that may be due to the enrolment of hospitalized patients with a mean age >50 years and multiple comorbidities. Although PE is the leading cause of death in patients with VTE, and obesity is commonly associated with various comorbidities, it has been recently reported a lower rate of mortality in obese patients with VTE than in non-obese patients, condition called the obesity paradox [8]. We could not assess this situation since we have not designed a prospective study.

Numerous studies have shown that advanced age is an independent risk factor for VTE, due to the increased blood coagulability and higher prevalence of other risk factors (such as malignancy, immobilization, hospitalization); the prevalence of VTE is age dependent in both obese and non-obese patients [2,8,10,15-17]. We found a higher risk of VTE in obese patients aged >50 years compared to those younger than 50 years old (OR: 6.142 respective 3.122).

Gender influences also the occurrence of VTE: female patients during the child-bearing years present a higher rate of VTE compared to men [18]. Sex-specific factors may also influence the risk stratification models as well as the presenting location of acute DVT: distal DVT, associated with a lower risk of PE, occurs predominantly in women [19]. We found a higher frequency of VTE in men aged >50 years compared to women, whereas men and women aged <50 years presented similar frequency of VTE (10.47% respective 6.54%). An explanation of this finding is the admission of pregnant women with comorbidities especially at the Department of Obstetrics and Gynecology; among 382 patients with VTE included in this study, only 9 cases (2.35%) were represented by pregnant or postpartum patients. Based upon the large cohort studies, it may be considered that the incidence of first VTE is approximately equal in both female and male, whereas the recurrent VTE occurs with a higher rate in men than in women; the overall age-adjusted incidence rate is slightly higher in men than women, with a male to female ratio = 1.2:1 [16,17]. Our findings show an overall 1.4-fold increased risk of VTE in male than in female patients (OR=5.69, respective 3.96).

VTE is the result of interaction of multiple risk factors. We have not studied genetic risk factors, which represent a limitation of this study. Recent data show that thrombophilia testing is not required in majority of the cases and should be performed only in selected patients, presenting: VTE at a young age, family history of VTE, VTE associated with weak provoking factors at a young age, recurrent VTE, and VTE in an unusual site [20]. Other limitations of this study are the followings: no distinct analysis of the association of obesity with VTE as the main reason of the admission, respective with VTE that occurred during hospitalization, the retrospective design without the follow-up of the cases that could have also offered data about recurrent thrombosis in obese patients. The association of obesity and recurrent VTE is controversial: some studies found an association whereas others did not [7,21,22; respective 23, 24].

Numerous studies identified obesity as an independent risk factor for VTE in population-based studies, outpatients, and in patients discharged from hospitals, taking into account other cardiovascular risk factors: hypertension, dyslipidemia, impaired glucose metabolism, smoking, age, hormonal therapy [2,9,16,25]. Our multivariate analysis, which included risk factors significantly associated with VTE (age, history of VTE, smoking, prolonged immobilization, varicose veins, COPD, heart failure, stroke, malignancy and recent surgery) showed obesity as an independent risk factor for both women and men. A potential association between VTE and atherosclerosis, conditions that share several risk factors, has been described [16,17,25,26]. Although there are conflicting results regarding the associations between VTE and diabetes mellitus, hypertension and dyslipidemia, obesity has consistently been identified as a risk factor associated with both arterial and venous thrombosis [17,25,26].

The main physiopathological background of the elevated thrombotic risk in obesity is represented by inflammation; C-reactive protein (CRP), a sensitive marker of inflammation, may represent the common pathway for the risk of arterial and venous thrombosis in obesity [27]. Recently it has been shown that the association between BMI and VTE is partially mediated by CRP and the association between CRP and VTE is stronger in obese women than in obese men [27,28]. Other associations between VTE and markers of inflammation (interleukin 6, interleukin 8, tumor necrosis factor-alpha) have been described; these cytokines induce the expression of tissue factor and inflammatory mediators may initiate the extrinsic coagulation pathway leading to a pro-coagulant state [29]. The disruption of the balance between prothrombotic adipokines (leptin, plasminogen activator inhibitor-1) and antithrombotic adipokines (adiponectin, apelin) in obesity contributes also to the occurrence of thrombosis [6]. A recent study found a causal association between genetically predicted high BMI and VTE, suggesting that reducing obesity may decrease the incidence of VTE [30]. Several genetic risk scores, assessing the overall genetic predisposition and the risk of VTE, may be applied in thromboprophylaxis in the future [17]. We have not studied the correlations between obesity, VTE, inflammatory markers and genetic polymorphisms, the focus being on the clinical data regarding the obesity in hospitalized patients.

The interaction of obesity with at least one of the risk factors significantly associated with VTE led to an almost double risk of VTE compared to the intervention of obesity alone; numerous studies show the increased thrombotic risk in case of the interplay between obesity and other risk factors [2,8,16]. Taking into account the intervention of multiple risk factors, various risk assessment models have been created; obesity is a parameter included in the risk stratification for VTE in cancer patients (Khorana score), in patients hospitalized for acute medical illness and postoperative cases (after total hip arthroplasty) [16,31].

Considering the current increasing trends in obesity, with a projected prevalence of ≥40% of total population in Romania by 2025, and the association with the thrombotic risk, it is expected that the incidence of VTE will rise, justifying a preventive strategy [8,11,32]. According to our findings, this should be addressed to medical and surgical hospitalized patients with obesity, especially in cases aged>50 years, with severe obesity and associated comorbidities. Taking into account the causal relationship between obesity and VTE, effective policies and interventions fighting obesity are likely to reduce the incidence of VTE [30,32].

Future research should be directed to clarify the dose-dependent effect on the interactions between obesity and other risk factors (such as hormone therapy, alcohol consumption), the role of the genetic risk scores and the potential utility of anti-inflammatory therapy in thromboprophylaxis in obesity as well as the proper anticoagulant regimens according to the class of obesity [2,7,33,34].

Conclusions

Obesity is a common, moderate and independent risk factor for VTE in both female and male patients. The risk increases with increasing BMI. The risk of VTE is higher in obese patients aged >50 years compared to those younger than 50 years old. The interaction between obesity and other risk factors doubles the risk of VTE.

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