Elevated body fat is a risk factor for venous thromboembolism and thrombotic complications

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Abstract

**Objective:** The aim of the study is to analyze the relationship between body composition and BMI with venous thromboembolism (VTE) and major complications: recurrence and post-thrombotic syndrome.

**Patients and methods:** We performed a case-control study of a group of patients with VTE (n=138) and a control group (n=127) with no history of thrombosis. BMI was calculated using the formula: BMI=weight (kg)/height$^2$ (m). The body composition of each subject was obtained by bioelectrical impedance analysis using the TBF 300a analyzer.

**Results:** Compared to subjects with BMI<25, patients with BMI>30kg/m$^2$ had more than a five-fold increased risk of developing a thrombotic event (OR: 5.47; 95% CI: 2.56-12.22) and patients with BMI between 25-30 kg/m$^2$ had a threefold increased risk  (OR: 2.95; 95% CI: 1.58-5.68). Patients with high body fat% had more than twice the risk of having a thrombotic event (OR: 2.72; 95% CI: 1.54-4.91). Higher body fat% was associated with an increased thrombotic risk in women (OR: 9.48; 95% CI: 4.16-23.82) but not in men (OR: 0.52; 95% CI: 0.20-1.31).

**Conclusion:** Our results suggest that patients with elevated percentage of body fat are in a higher risk of develop a venous thrombotic event.

**Keywords:** Venous thromboembolism, obesity, BMI, body composition, recurrence, post-thrombotic syndrome

Background

Venous thromboembolism (VTE) is a disabling condition with a high probability of recurrence and potentially fatal. This condition is characterized by the formation of a thrombus in the venous system, preceded or followed by an inflammatory response of the vessel wall. When part of the clot breaks off, it can migrate through the circulatory system to the pulmonary artery, causing a pulmonary embolism (PE). The VTE is characterized by an acute presentation, but can be considered a chronic disease due to the complications in its natural course and because of the possibility of recurrence. Despite advances in anticoagulatory therapy, VTE has still a high incidence. A significant number of the cases could have been avoided with the establishment of adequate anticoagulatory prophylaxis [1]. In developed countries, thrombosis, considering the venous and arterial, is the leading cause of mortality in adult, exceeding more than 3 times a neoplastic disease deaths [1-6]. The VITAE study estimated that in Europe there are more than 1.5 million cases annually, with 435000 cases of PE and 684000 of symptomatic deep venous thrombosis (DVT) [1].

The most common complications of VTE are post-thrombotic syndrome (PTS) and pulmonary hypertension. Post-thrombotic syndrome generates a high rate of sick leaves and produces a variable degree of morbidity in patients. The other major complication of VTE is death by pulmonary embolism, which occurs in approximately 1-2% of patients [7,8]. PE has an incidence of 6% in the DVT in upper limbs (DVT-UL) compared to 15-32% in the DVT in lower limbs (DVT-LL). Post-thrombotic syndrome has an incidence of 5% in the upper extremities compared to 56% in the lower extremities [9]. Another complication of venous thrombosis are the recurrent events, presented in 2-5% of DVT-UL and 10% of the DVT-LL.

Obesity is a multifactorial chronic disease associated with several complications and increased mortality. In addition, obesity is predisposing risk factors for different diseases including type 2 diabetes, certain lung diseases, sleep apnea, pulmonary hypoventilation syndrome, osteoarthritis, cancer or certain gynecological disorders [10-12].

Currently, BMI is collected routinely in many of the studies on risk factors for VTE, and there are some studies that show an increased thrombotic risk with in patients with elevated BMI [13-16]. Obesity may increase the risk of thrombosis in
different ways: via leptin, by increasing the activity of the coagulation cascade and by decreasing fibrinolysis. Leptin is a peptide produced by adipose tissue and it acts as a hormone in the hypothalamus, reducing appetite. In cases of obesity, leptin levels are elevated, so it creates a certain resistance to its action. Leptin has been associated with ADP-dependent platelet aggregation [17] and its levels correlate with levels of antitgenic tPA (tissue plasminogen activator) [18]. Higher levels of tPA signify elevated concentrations of PAI-1.

Other changes are the result of the insulin resistance that occurs in obese patients, and others are due to excess of fat per se. One of them is high fibrinogen levels (hyperfibrinogenemia). Dysfunctional adipocytes produce IL-6, a direct stimulator of fibrinogen synthesis in the liver, contributing to increased plasma fibrinogen levels [19,20]. In addition, hyperinsulinemia stimulates the production of PAI-1 in the liver, and the adipose tissue can also become a producer. Elevated levels of PAI-1 are associated with less fibrinolysis and elevated plasma fibrinogen levels [21].

Also, a higher percentage of body fat, especially in the abdominal area, may limit venous return, resulting in increased intra-abdominal pressure and decreased blood velocity in the femoral vein in many obese patients [18].

Body composition
BMI is the most widely used indicator of obesity for population samples, although there are some limitations to BMI interpretation. Some diseases and pathological conditions are accompanied by changes in the composition of the different body compartments such as fat-free mass, fat mass and total body water [22].

An excess of body fat plays a central role in the development of some diseases such as metabolic syndrome because of its relationship with lipids and blood pressure. Traditionally, BMI is considered a good indicator of obesity, but BMI is only the relationship between body weight and height. Body weight is determined by both fat mass and muscular mass, so people with high muscle development BMI is uncertain.

To study the implication of obesity in the development of thrombosis, it is important differentiate between central obesity and peripheral obesity. Central obesity is defined as the deposition of fat in the trunk and visceral adipose tissue, and peripheral obesity refers to the accumulation of fat in the gluteal-femoral area. In the development of VTE and thrombotic complications—mainly in the lower limbs—peripheral obesity seems to play a more important role, blocking or hindering venous return.

Electrical bioimpedance has certain advantages over other techniques for the study of body composition, such as ease of use, cost, and safety. By sending a small electrical current through the body, we can calculate the resistance opposed to its flow by the tissues (impedance), and thus calculate body composition [23]. This technique is based on the higher electrolyte content and greater conductivity of muscle mass than fat.

Patients and methods
We performed a case-control study involving a group of patients with VTE and a control group with no history of thrombosis. This work was conducted in strict adherence of the Declaration of Helsinki and data protection laws (Law 15/1999 on Protection of Personal Data) and the protection of patient rights (Law 15/2002). In addition informed consent was obtained from all participants. This study was reviewed and approved by the Clinical Research Ethics Committee of the University Hospital Fundación Jiménez Díaz UH-FJD, where the studies were conducted.

The study included 138 patients with VTE (DVT-LL or PE) referred to the Hematology Department either for thrombophilia study or for control of coagulant therapy between January, 2009 and January, 2012. Following current hospital protocol, diagnosis of VTE and VTE recurrence were performed by physical examination (color and skin lesions, edema and asymmetry, peripheral pulses, characteristics of edema, skin temperature, etc.), and were confirmed by objective tests. Definitive diagnosis of DVT was based on the results of Doppler ultrasound imaging. Cases of PE were diagnosed after a high-probability V/Q scan, and in cases in which was necessary a pulmonary angiography to confirm the diagnosis. The group of patients was subjected to a mean follow-up of 40 (±21) months in order to evaluate the occurrence of thrombotic complications. Diagnosis of PTS and the presence of residual thrombus were confirmed by objective testing (Doppler ultrasound) 3, 6 and 12 months after the acute event. Post-thrombotic syndrome was defined according to the CEAP clinical scale [24,25]. To analyze the relationship of obesity-related parameters with recurrence and PTS, we compared the group of patients with recurrent events or PTS, with the group of patients who did not develop recurrence or PTS, excluding the group of subjects with no history of thrombosis. Patients who were participating in a clinical trial at the time of this study, those in whom monitoring was not possible and patients who did not provide consent were excluded. We included a control group of 127 unselected subjects from the same demographic area and same race as the group of patients with VTE. The control group was obtained by reviewing the medical histories of patients admitted to different departments of the UH-FJD. We included those patients who had no previous or current history of VTE or vascular disease (eg., myocardial infarction, ischemic heart disease, hypertensive heart disease, atrial fibrillation, ictus, peripheral vascular disease, claudication).

Demographic variables, age and sex, as well as classic cardiovascular risk factors (dyslipidemia, smoking, hypertension and diabetes mellitus) were collected from each patient. Cardiovascular risk factors were defined as follows: dyslipidemia (total cholesterol>220 mg/dl, HDL<35 mg/dl, total cholesterol/HDL cholesterol>4.5 or triglycerides>200 mg/dl, in at least 3 successive determinations; or use of hypolipidemic drugs), hypertension (diastolic blood pressure>90 mmHg and/or
systolic blood pressure > 140 mmHg detected 24 hours after admission on several measurements, or use of antihypertensive drugs preadmission), diabetes mellitus (DM) (fasting glucose > 38 mg/dl or prior use of oral hypoglycemic medications or insulin), smoking (regular consumption of more than 10 cigarettes per day at the time of enrollment or two years prior).

Height and weight were measured for each patient and control subject. From these measurements, BMI was calculated using the formula: BMI = weight (kg)/height^2 (m). The measurements were performed on patients while they were wearing light clothing and barefoot. The weight measurement was obtained with a precision of 0.1 kg on a digital electronic scale. Our population was categorized according to their BMI as obese (BMI > 30 kg/m^2), overweight (25 < BMI ≤ 30 kg/m^2), normal weight (18 < BMI ≤ 25 kg/m^2) and underweight (BMI ≤ 18 kg/m^2) according to the cut-off points proposed by the WHO.

For the study of BMI two types of analysis was performed, firstly the mean value of BMI was compared between the patient and the control group. Furthermore, the incidence of VTE, recurrence and PTS was analyzed in two groups according to BMI, with reference to the group of subjects with BMI < 25 kg/m^2. These two groups were: 1) overweight: BMI: 25-30 kg/m^2 and 2) obesity: BMI > 30 kg/m^2.

Body composition
The body composition of each patient and control subject was obtained by bioelectrical impedance analysis using the TBF 300a analyzer (TANITA Corp., Arlington Heights, Japan). This protocol has been validated in several studies for different groups, including adults over 60 years [26] and postmenopausal women [27], among others. The measurements were performed with patients standing on the plates of the analyzer while wearing no shoes or socks. The analyzer measures body composition by using a continuous energy source that generates a stream of high frequency and low intensity (50 kHz, 500 µA) and with 4 pairs of bipolar electrodes. To calculate body composition, it was necessary to insert in the analyzer the variables: age, sex, height and physical activity.

Height measurements were collected prior to the calculation of BMI. The frequency of patients' physical activity was classified as standard or athletic based on the number of hours of activity they reported per week (standard, < 10 hours of exercise a week, and athletic, > 10 hours). All measurements were performed in duplicate with a one-minute gap between them.

For the study of body composition two types of analysis was performed, firstly the average value of body fat (BF) % and total BF (kg), in this case the mean values were compared between the patient group and the control group. Furthermore, the BF% was analyzed considering the ideal values supplied by the analyzer, so we compared the cases with high BF% versus who who had a normal BF% or low BF%. Finally, the amount of total BF (kg) was analyzed by comparing patients in the highest quartile (Q3 and Q4) to patients in the lowest quartile (Q1 and Q2).

Statistical analysis
We conducted a descriptive study of the discrete variables, calculating the frequency and percentage of occurrence of each parameter. Two analyses were conducted: the variables were analyzed quantitatively, and then were categorized to study the subset of patients with normal parameters compared to those with high levels of weight, BMI and BF%. Descriptive statistics were calculated (mean, median, standard deviation and lower and upper quartiles) for quantitative variables. In the univariate logistic regression model, the presence or absence of thrombosis was taken as a dependent variable. All comparisons were performed with a significance level of 0.05. The magnitude of association was calculated by the OR, estimated by logistic regression with confidence intervals at 95% (95% CI). Comparisons of quantitative variables were performed using Student's t test or Mann -Whitney U test, depending on whether the variable was normally distributed or not. To study the association of categorical variables with VTE, contingency tables were obtained, and chi-square or Fisher's were used. We conducted a multivariate logistic regression analysis adjusting for age, sex and cardiovascular risk factors (hypertension, DM, dyslipidemia and smoke). To compare the differences between the groups, we performed a test of homogeneity, the OR was considered significant at p < 0.05. Statistical analysis of the data was performed with Stata v 10 (StatCorp LP, USA).

Results
The mean age of the patients was 54.30 (±17.44) years, while in the controls it was 59.02 (±18.32) years (p = 0.0201). The patient group was composed of 42.3% (n = 83) of men while in the control group men represented 39.4% (n = 50). The baseline characteristics of patients and controls are shown in Table 1.

Body mass index
All subjects included in the study were classified by BMI: normal weight (BMI < 25 kg/m^2), overweight (25 < BMI ≤ 30 kg/m^2) and obesity (BMI > 30 kg/m^2). None of the patients or controls included in the study had BMI values < 18 kg/m^2. High BMI was found in 39.2% of patients with VTE. The mean BMI was significantly higher in the patient group (28.26 ± 5.29 kg/m^2 vs 26.31 ± 5.29 kg/m^2; OR: 1.07, 95% CI: 0.007 - 1.09, p = 0.0021).

When we estimated the association between BMI and VTE, the analysis showed that patients with BMI > 30 kg/m^2 had a 5-fold greater risk of developing a thrombotic event (OR: 5.47; 95% CI: 2.56-12.22), whereas in patients with BMI between 25-30 kg/m^2 (OR: 2.95; 95% CI: 1.58-5.68), the risk was increased nearly threefold. The association with BMI remained after performing the analysis adjusting for age and sex (Table 2).

Body composition
BF% was determined for 138 patients and 127 controls. After
Table 1. Baseline characteristics of patients and controls.

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=127)</th>
<th>Patients (n=138)</th>
<th>p</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>59.02 (18.32)</td>
<td>52.62 (15.06)</td>
<td>0.002</td>
<td>0.98 (0.96-0.99)</td>
</tr>
<tr>
<td>Sex (women/men) n (%)</td>
<td>77/50 (60.6/39.4)</td>
<td>113/83 (57.7/42.3)</td>
<td>0.166</td>
<td>1.41 (0.87-2.31)</td>
</tr>
<tr>
<td>BMI (SD)</td>
<td>26.3 (5.3)</td>
<td>27.8 (6.2)</td>
<td>0.004</td>
<td>1.07 (1.02-1.13)</td>
</tr>
<tr>
<td>Dyslipidemia n (%)</td>
<td>24 (18.9)</td>
<td>84 (43.8)</td>
<td>&lt;0.0001</td>
<td>3.87 (2.72-5.56)</td>
</tr>
<tr>
<td>Hypertension n (%)</td>
<td>30 (23.69)</td>
<td>29 (21)</td>
<td>0.610</td>
<td>0.86 (0.48-1.54)</td>
</tr>
<tr>
<td>Diabetes Mellitus n (%)</td>
<td>13 (10.2)</td>
<td>6 (4.3)</td>
<td>0.071</td>
<td>0.39 (0.14-1.04)</td>
</tr>
<tr>
<td>Tobacco n (%)</td>
<td>17 (13.4)</td>
<td>40 (29)</td>
<td>0.025</td>
<td>2.64 (1.43-5.06)</td>
</tr>
<tr>
<td>Obesity * n (%)</td>
<td>19 (15)</td>
<td>38 (27.5)</td>
<td>&lt;0.0001</td>
<td>5.47 (2.56-12.22)</td>
</tr>
</tbody>
</table>

*Consider obesity as a BMI >30 Kg/m². ‡ OR adjusted by sex and age.

Table 2. Association between BMI and VTE.

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>Crude OR</th>
<th>Adjusted OR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(95% CI)</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>25-30</td>
<td>2.37</td>
<td>2.95</td>
</tr>
<tr>
<td>&gt;30</td>
<td>3.56</td>
<td>5.47</td>
</tr>
</tbody>
</table>

BMI: body mass index.
*Adjusted by sex, age and cardiovascular risk factors (dislipidemia, tobacco, DM and hypertension).

Table 3. Association between BMI and VTE by sex.

<table>
<thead>
<tr>
<th>WOMEN</th>
<th>Mean±SD</th>
<th>VTE (n=138) Controls (n=127)</th>
<th>Mean±SD</th>
<th>VTE (n=138) Controls (n=127)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>27.6±5.5</td>
<td>25.6±5.2</td>
<td>1.09 (1.02-1.18)</td>
<td>0.007</td>
</tr>
<tr>
<td>MEN</td>
<td>Mean±SD</td>
<td>VTE (n=138) Controls (n=127)</td>
<td>Mean±SD</td>
<td>VTE (n=138) Controls (n=127)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.0±6.9</td>
<td>27.4±5.3</td>
<td>1.06 (0.98-1.14)</td>
<td>0.1475</td>
</tr>
</tbody>
</table>

BMI: body mass index.
*Adjusted by sex, age and cardiovascular risk factors (dislipidemia, tobacco, DM and hypertension).

For BF (kg), a significant association was found in two analyzed quartiles (Table 4). When the patients were analyzed by sex, the results revealed some differences between men and women. Table 5 shows the results obtained in the analysis adjusted for age, sex and thrombotic risk factors. Higher BF% was associated with an increased thrombotic risk only in women (OR: 9.48; 95% CI: 4.16-23.82).

Thrombotic complications
The relationship between obesity and the occurrence of recurrent thrombotic events was analyzed. Of the total group, 60 patients developed recurrent events during the follow-up period. We estimated the association of recurrence with BMI, BF% and the amount of BF (kg). We found no statistically significant association of either of these variables with
Discussion

We conducted a case-control study in which we analyzed the relationship between obesity and venous thromboembolic disease. The study has some limitations, since BMI and body composition can vary over time. In our study, these parameters were collected only once—at the time of patient inclusion—so possible variations occurring in the association with VTE have not been accounted for. On the other hand, excess body weight evaluated as BMI is not a good estimate of fat distribution. Indicators of central obesity, including waist circumference or waist/hip ratio, may provide complementary information. Some of the odds ratios presented in this manuscript indicate a certain degree of association between BMI and BF%, and VTE, but suffer from statistical uncertainty (very wide 95% confidence intervals). This is an important limitation of the study.

BMI analysis showed that patients with BMI between 25-30 kg/m² have twice the thrombotic risk than subjects with BMI<25 kg/m², while patients with BMI>30 kg/m² have five times the risk of developing a thrombotic event. When analyzing the variables according to sex, we found that the thrombotic risk associated with high BMI was greater in women than in men.

### Table 4. Association of body fat and VTE.

<table>
<thead>
<tr>
<th></th>
<th>VTE (n=138)</th>
<th>Controls (n=127)</th>
<th>OR* (95% CI); p</th>
<th>OR* (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>BF%</td>
<td>29.8±9.71</td>
<td>29.1±9.00</td>
<td>1.05 (1.02-1.09); 0.004 High</td>
<td>2.72 (1.54-4.91) 0.0005</td>
<td></td>
</tr>
<tr>
<td>BF (kg)</td>
<td>23.5±9.98</td>
<td>21.8±8.87</td>
<td>1.03 (1.00-1.06); 0.025 Q3</td>
<td>2.04 (1.09-3.89) 0.011</td>
<td></td>
</tr>
<tr>
<td>Q4</td>
<td></td>
<td></td>
<td>2.57 (1.31-5.19)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BF%: percentage of body fat, BF (kg): body fat (kg). Q3: third quartile (21.1-27.9) kg, Q4: forth quartile (>27.9) kg. *Adjusted by sex, age and cardiovascular risk factors (dislipidemia, tobacco, DM and hypertension).

### Table 5. Relationship of body composition with VTE in men and women.

#### WOMEN

<table>
<thead>
<tr>
<th></th>
<th>VTE (n=138)</th>
<th>Controls (n=127)</th>
<th>OR* (95% CI); p</th>
<th>OR* (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>BF%</td>
<td>35.4±8.2</td>
<td>32.5±8.4</td>
<td>1.07 (1.02-1.12); 0.004 High</td>
<td>9.48 (4.16-23.82) &lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>BF (kg)</td>
<td>26.0±10.0</td>
<td>23.2±9.0</td>
<td>1.04 (1.01-1.08); 0.0236 Q3</td>
<td>2.47 (1.06-5.92) 0.017</td>
<td></td>
</tr>
<tr>
<td>Q4</td>
<td></td>
<td></td>
<td>3.14 (1.37-7.50)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BF%: percentage of body fat, BF (kg): body fat (kg). Q3: third quartile (21.1-27.9) kg, Q4: forth quartile (>27.9) kg. *Adjusted by sex, age and cardiovascular risk factors (dislipidemia, tobacco, DM and hypertension).

#### MEN

<table>
<thead>
<tr>
<th></th>
<th>VTE (n=138)</th>
<th>Controls (n=127)</th>
<th>OR (95% CI); p</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>BF%</td>
<td>23.7±7.2</td>
<td>24.0±7.3</td>
<td>1.02 (0.96-1.08); 0.519 High</td>
<td>0.52 (0.20-1.31) 0.1658</td>
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<tr>
<td>BF (kg)</td>
<td>20.7±9.3</td>
<td>19.8±8.4</td>
<td>1.01 (0.96-1.06); 0.699 Q3</td>
<td>1.45 (0.52-4.14) 0.616</td>
<td></td>
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<tr>
<td>Q4</td>
<td></td>
<td></td>
<td>1.70 (0.47-6.68)</td>
<td></td>
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</tbody>
</table>

BF%: percentage of body fat, BF (kg): body fat (kg). Q3: third quartile (21.1-27.9) kg, Q4: forth quartile (>27.9) kg. *Adjusted by sex, age and cardiovascular risk factors (dislipidemia, tobacco, DM and hypertension).

### Table 6. Association of BMI, BF% and BF (kg) with thrombotic recurrence.

<table>
<thead>
<tr>
<th></th>
<th>Recurrence (n=60)</th>
<th>No recurrence (n=78)</th>
<th>OR* (95% CI); p</th>
<th>OR* (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>27.8±6.9</td>
<td>27.7±5.5</td>
<td>1.00 (0.94-1.06); 0.995 25-30</td>
<td>0.87 (0.35-2.14) 0.946</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;30</td>
<td></td>
<td>0.87 (0.35-2.14) 0.946</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BF%</td>
<td>28.4±10.7</td>
<td>31.0±8.7</td>
<td>0.96 (0.91-1.00); 0.076 High</td>
<td>0.68 (0.25-1.55) 0.313</td>
<td></td>
</tr>
<tr>
<td>BF (kg)</td>
<td>23.0±10.6</td>
<td>23.9±9.5</td>
<td>0.99 (0.96-1.03); 0.719 Q3</td>
<td>0.84 (0.35-1.99) 0.919</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Q4</td>
<td></td>
<td>0.97 (0.39-2.37)</td>
<td></td>
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</tbody>
</table>

OR adjusted for age and sex. BF%: percentage of body fat, BF (kg): body fat (kg). Q3: third quartile (21.1-27.9) kg, Q4: forth quartile (>27.9) kg. *Adjusted by sex, age and cardiovascular risk factors (dislipidemia, tobacco, DM and hypertension).
By analyzing the relationship of body fat (%) with VTE, a significant association was found in women, but not for men. VTE patients with a high percentage of %BF had a two-fold higher risk than those in whom BF% was within the ideal values (OR: 2.72). When the analysis was performed by sex, the risk associated with elevated BF% in women was OR: 9.48.

The pathophysiological mechanisms by which obesity increases the risk for thrombosis are different: inflammation, oxidative stress, dyslipidemia and insulin resistance. It also seems to have direct effects on the coagulation cascade and the fibrinolytic system. The physical characteristics of obese patients may contribute to the risk of VTE. More body fat especially abdominal fat- may limit venous return. Obese patients have elevated intra-abdominal pressure and decreased blood flow in the femoral vein [28]. The study of the parameters used to characterize venous flow in the lower extremities of obese and non-obese healthy subjects has shown significant differences between the two groups, being lower in the obese group. This suggests a mechanical role of the abdominal adipose tissue [29].

Current data suggest that fat mass, regardless of its distribution in the body, is positively associated with VTE. Adipose tissue secretes biologically active molecules, hormones, cytokines and growth factors [30]. Between the molecules produced by adipose tissue highlights leptin, this molecule is capable of associating with ADP, inducing platelet aggregation [18]. Moreover, leptin has been shown to correlate with the tPA antigen [17], higher concentrations of inhibitor PAI-1 reduce fibrinolysis, thus favoring the prothrombotic state. Many of the substances secreted by fat tissue are associated with procoagulant activity or inhibition of fibrinolysis. Therefore, it is possible that both the central and peripheral obesity are risk factors for venous thrombosis.

The Framingham Offspring Study evaluated cardiovascular risk factors and their association with prothrombotic factors in 3,230 subjects [31]. Increased BMI and waist-hip ratio were associated with elevated levels of fibrinogen and PAI-1. Furthermore, it has been shown that BMI and waist-hip ratio levels correlate positively with FVII, FVIIIc, fibrinogen and vWF [31,32].

The results of several studies coincide with ours, and corroborate that overweight is associated with an increased risk of thrombosis, both arterial [33] and venous [34], independently of other risk factors. A Danish population study evaluated the association of different anthropometric parameters (weight, BMI, waist circumference, hip circumference, fat mass) with thrombosis, and found that the risk of VTE increased 2 to 3 times in patients with BMI in the highest quartile compared to the lowest [14]. Many other studies support these findings [33,35,36]. One of the most important studies was published by Ageno et al., in 2008. This meta-analysis reviewed the literature from 1386 to 2006, and included 8 studies evaluating the association of obesity (BMI=30kg/m²) and thrombosis. The final OR was 2.33 (95% CI: 1.68 -2.34) [35].

Few studies have evaluated the relationship of obesity with venous thrombosis using parameters other than BMI. Our results are in agreement with those published by Severinsen et al., These authors studied 641 patients with DVT, and estimated a two-fold thrombotic risk in patients with elevated fat mass (kg) (HR: 2.33 for women, and HR 1.89 for men) [15]. In a large case-control study, a positive association between VTE and body weight was found, in addition to BMI [37]. This conclusion resembles that of a study of males that showed a greater risk of VTE for a waist circumference above 100 cm [38].

**Thrombotic complications**

No association with thrombotic recurrence was found for any of the obesity-related parameters included in the study. However, the percentage of patients with BMI>25 kg/m² (77.6%) and elevated BF% (61%) showed a tendency in the relationship between obesity and recurrent thrombosis. The outcome may have been skewed by the low number of patients with recurrence for whom it was possible to determine these parameters could influence. Our results are similar to those obtained by Romuald et al., in 100 patients, of this 58 had abdominal obesity and 42 did not. The main conclusion of the study was that abdominal obesity affects the risk of recurrence [39].

By contrast, a study of 1,107 patients with a mean follow-up of 46 months showed that 168 subjects who had developed

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**Table 7. Association of BMI, BF% and BF (kg) with PTS.**

<table>
<thead>
<tr>
<th></th>
<th>Mean±SD</th>
<th>OR* (95% CI); p</th>
<th>OR* (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=51</td>
<td></td>
<td>25-30</td>
<td>0.30-2.56</td>
<td></td>
</tr>
<tr>
<td>No PTS</td>
<td>n=87</td>
<td>&gt;30</td>
<td>0.54-4.15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BF%</td>
<td>0.99 (0.94-1.03); 0.549</td>
<td>High</td>
<td>0.99 (0.37-2.44); 0.945</td>
</tr>
<tr>
<td>Q3</td>
<td>BF (kg)</td>
<td>1.00 (0.96-1.04); 0.949</td>
<td>Q3</td>
<td>1.75 (0.72-4.32); 0.463</td>
</tr>
<tr>
<td>Q4</td>
<td></td>
<td>1.34 (0.53-3.39)</td>
<td>Q4</td>
<td></td>
</tr>
</tbody>
</table>

BF%: percentage of body fat, BF (kg): body fat (kg). Q3: third quartile (21,1-27,9) kg, Q4: forth quartile (>27,9) kg. *Adjusted by sex, age and cardiovascular risk factors (dislipidemia, tobacco, DM and hypertension).
recurrent events had a significantly higher mean BMI than that of normal-weight patients (28.5 kg/m² vs. 26.9 kg/m², p=0.01); the study found that the risk of recurrence was 1.3 for overweight patients (95% CI: 0.9-1.9) and 1.6 for obese patients (95% CI: 1.1-2.4) [38]. According to this study by Eichinger et al., the relationship between BMI and thrombotic recurrence is linear, so small changes in body weight could result in a significant reduction in risk of recurrence. The decreased risk of recurrence could be eliminated if all patients in the study had a normal weight was 26.8% [40].

When analyzing the relationship with PTS, we also found no differences between patients and controls, and there were no differences between men and women. Although no significant differences were found, 80% of patients with PTS had a BMI>25 kg/m². The high percentage of patients with elevated BMI in the group of subjects with VTE (73%) means that the differences are not significant, but reflects once again the importance of obesity and overweight in these patients. The relationship of obesity and overweight in PTS has been studied by different groups. A prospective cohort of 83 consecutive patients with DVT was the subject of a study that assessed weight gain and changes in waist circumference 12 months after the acute event as well as the existence of symptoms compatible with PTS. The BMI of the subjects who developed PTS was higher (29.6 kg/m² vs. 27.2 kg/m², p=0.02) [41]. Another study conducted in young women showed that BMI>22 kg/m² was associated with the risk of PTS (OR: 4.6) [42]. These results have been subsequently confirmed by other study in a group of 244 patients with DVT, BMI>25 kg/m² was related to the development of PTS, with an OR of 1.14 [43].

Conclusions

We found statistically significant positive association between BMI, BF% and BF (kg) and VTE, we have also observed a trend in the relationship of these parameters with thrombotic complications. However, further studies are needed to explain the mechanism underlying the associations.

List of abbreviations

BF: body fat
BMI: body mass index
DM: diabetes mellitus
DVT: deep venous thrombosis
DVT-LL: deep venous thrombosis of the lower limbs
DVT-UL: deep venous thrombosis of the upper limbs
HDLC: high density lipoproteins cholesterol
HR: hazard ratio
UH-FJD: University Hospital Fundación Jiménez Díaz
IL-6: Interleukina 6
OR: odds ratio
PAI-1: plasminogen activator inhibitor 1
PE: pulmonary embolism
PTS: post-thrombotic syndrome
TC: total cholesterol
TG: triglycerides

References


