Overweight, Obesity, and the Risk of Recurrent Venous Thromboembolism

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Background: Excess body weight is a risk factor for a first venous thromboembolism. The impact of excess body weight on risk of recurrent venous thrombosis is uncertain.

Methods: We studied 1107 patients for an average of 46 months after a first unprovoked venous thromboembolism and withdrawal of anticoagulant therapy. Excluded were pregnant patients, those requiring long-term antithrombotic treatment, and those who had a previous or secondary thrombosis, natural coagulation inhibitor deficiency, lupus anticoagulant, or cancer. Our study end point was symptomatic recurrent venous thromboembolism.

Results: A total of 168 patients had recurrent venous thromboembolism. Mean (SD) body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) was significantly higher among patients with recurrence than among those without recurrence: 28.5 (6.0) vs 26.9 (5.0) (P = .01). The relationship between excess body weight and recurrence was linear; the adjusted hazard ratio for each 1-point increase in BMI was 1.044 (95% confidence interval [CI], 1.013-1.076) (P < .001). Four years after discontinuation of anticoagulant therapy, the probability of recurrence was 9.3% (95% CI, 6.0%-12.7%) among patients of normal weight and 16.7% (95% CI, 11.0%-22.3%) and 17.5% (95% CI, 13.0%-22.0%) among overweight and obese patients, respectively. Compared with patients of normal weight, the hazard ratio of recurrence adjusted for age, sex, factor V Leiden, prothrombin G20210A mutation, high factor VIII levels, and type of initial venous thromboembolic event was 1.3 (95% CI, 0.9-1.9) (P = .20) among overweight patients and 1.6 (95% CI, 1.1-2.4) (P = .02) among obese individuals. The population attributable risk corresponding to excess body weight was 26.8% (95% CI, 5.3%-48.2%).

Conclusion: Excess body weight is a risk factor of recurrent venous thromboembolism.

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Excess body weight is a major health problem throughout the industrialized world. Despite many efforts to promote weight loss, the prevalence of overweight and obesity has constantly risen over the years. According to estimates from the National Health and Nutrition Examination Survey (NHANES) conducted in 2003 and 2004, 34% of US adults are overweight, and an additional 32% are obese. There is now compelling evidence for a close association between excess body fat and numerous adverse health outcomes, including diabetes, hypertension, coronary heart disease, ischemic stroke, or cancer. Importantly, 2 recent studies from Korea and the United States showed an association between excess body weight and increased risk of death.

Excess body weight is also a risk factor of venous thromboembolism. In the Framingham study, women who died from pulmonary embolism had higher weights than women who died from other causes. In the Nurses’ Health study, a body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) of 29 or higher was an independent risk factor for pulmonary embolism. In a study from Sweden, men with a waist circumference of at least 100 cm had a 4-fold higher risk of venous thromboembolism than men with a waist circumference of less than 100 cm. In a population-based case-control study from the Netherlands, obesity conferred a 2-fold increased risk of venous thromboembolism than men with a waist circumference of less than 100 cm. In a retrospective hospital discharge set, obese men and women had 2- and 3-fold increased risks of venous thromboembolism, respectively. Excess body weight is also a risk factor for venous thromboembolism among medical and surgical patients.
Venous thromboembolism is a common disease with an incidence of 1.4 per 1000 person-years. Its major clinical complications are recurrence of disease (which is fatal in approximately 5% of cases) and morbidity due to the postthrombotic syndrome. Important risk factors of recurrent venous thromboembolism are male sex, cancer, antiphospholipid syndrome, previous thrombosis, deficiency of a natural coagulation inhibitor, hyperhomocysteinemias, and high factor VIII levels. In a retrospective, population-based US study, a 10-point increase in BMI was found to increase the risk of recurrent venous thromboembolism by 24%. In another retrospective analysis, increased BMI was associated with a higher probability of recurrent venous thromboembolism among young women. In a small study from Spain, a nonsignificant 1.9-fold increase in the risk of recurrence was seen in patients with a BMI of more than 30 compared with those with a lower BMI.

It was our aim to assess the association between excess body weight and symptomatic recurrent venous thromboembolism in a large cohort of 1107 patients who were prospectively observed after their first unprovoked venous thromboembolism.

PATIENTS AND STUDY DESIGN

The ethics committee of the Vienna University Hospital approved the study, and all patients provided written informed consent prior to inclusion.

The Austrian Study on Recurrent Venous Thromboembolism (ASSET) is an ongoing prospective cohort study involving 2 primary care hospitals and 2 academic tertiary care centers. Between July 1992 and December 2006, 3257 consecutive patients (older than 18 years) with deep vein thrombosis of the leg and/or pulmonary embolism, who had been treated with anticoagulants for at least 3 months, were screened. Of these patients, 2150 were excluded because of surgery, trauma, or pregnancy within the previous 3 months (n=507); previous venous thromboembolism (n=441); deficiency of antithrombin, protein C, or protein S (n=85); presence of the lupus anticoagulant (n=81); cancer (n=484); or requirement for long-term antithrombotic treatment (n=493). Thirty-three patients with high factor VIII levels who participated in a trial of long-term anticoagulation therapy were also excluded, as were 26 patients with combined or homozygous genetic defects. All patients had been treated initially with unfractionated or low-molecular-weight heparin in therapeutic doses. All patients were treated at the discretion of their treating physician but received vitamin K antagonists for at least 3 months.

Patients entered the study at the time of discontinuation of anticoagulation therapy. At study entry, BMI was determined, and patients were categorized as normal (BMI <25), overweight (BMI ≥25 and <30), or obese (BMI ≥30). Patients were then seen at 3-month intervals during the first year and every 6 months thereafter. They received written information on the symptoms of venous thromboembolism and were instructed to report if such symptoms occurred. At each prescheduled visit, patients completed a standardized questionnaire designed to discover whether signs and symptoms of recurrent venous thromboembolism or postthrombotic syndrome had occurred since the last visit. A physical examination was performed, and venous blood was obtained. All women were strongly discouraged from using contraceptive pills whether or not venous thromboembolism was associated with hormonal birth control. During conditions associated with increased risk of thrombosis such as surgery or trauma, patients received routine heparin thromboprophylaxis.

DIAGNOSIS OF VENOUS THROMBOEMBOLISM

Diagnosis of deep vein thrombosis was established by a positive finding on venography or color duplex sonography (in case of proximal thrombosis). A positive finding included at least 1 of the following direct or indirect criteria: (1) a constant filling defect seen on 2 views; (2) an abrupt discontinuation of the contrast-filled vessel at a constant level of the vein; and (3) the absence of filling in the entire deep vein system (without a compression) with or without venous flow through collateral veins. A positive finding on color duplex ultrasonography included at least 1 of the following criteria for deep vein thrombosis: (1) visualization of an intraluminal thrombus in a deep vein and (2) incomplete or absent compressibility.

The diagnosis of pulmonary embolism was confirmed either by a positive finding on ventilation-perfusion scan, according to the criteria of the Prospective Investigation of Pulmonary Embolism Diagnosis, or by spiral computed tomography revealing 1 or more low attenuation areas that partly or completely filled the lumen of an opacified vessel. Patients with symptomatic pulmonary embolism and deep vein thrombosis were classified as having pulmonary embolism.

STUDY OUTCOMES

The end point of the study was recurrent symptomatic deep vein thrombosis confirmed by venography or color duplex sonography (in case of proximal thrombosis of the contralateral leg) or recurrent symptomatic pulmonary embolism confirmed by ventilation-perfusion scan and/or spiral computed tomography. Deep vein thrombosis was considered to have recurred if the patient had (1) a thrombus in the leg not affected by the previous thromboembolic event; (2) a thrombus in another deep vein in the same leg as the previous event; or (3) a thrombus in the same venous system as the previous event with proximal extension of the thrombus (if the upper limit of the original thrombus had been visible) or with a constant filling defect surrounded by contrast medium (if the original thrombus had not been visible). An adjudication committee consisting of independent radiologists established the diagnosis.

LABORATORY ANALYSIS

At study entry, blood was collected after fasting into 1/10 volume of 0.11 mM trisodium citrate and immediately centrifuged for 20 minutes at 2000g. The plasma was stored at –80°C. Screening for factor V Leiden and prothrombin G20210A and determination of antithrombin, protein C, protein S, factor VIII, factor IX, and fibrinogen levels was carried out as previously described. D-dimer and C-reactive protein levels were determined by high-sensitivity enzyme-linked immunoassay (Asserachrom D-Dimer; Roche, Grenzach, Germany) and nephelometry (Dade Behring, Marburg, Germany), respectively. The technicians were unaware of the patient characteristics at all times.

STATISTICAL ANALYSIS

Categorical data were presented as frequencies and percentages and compared between groups by the χ2 test. Continuous data were presented as mean (SD) or median (25th, 75th percentiles) and compared using Mann-Whitney tests. The cumu-
relative probability of recurrence was estimated according to the Kaplan-Meier method and compared between groups by the log-rank test. Patients without recurrence or who were lost to follow-up were treated as censored. Follow-up was stopped for patients who died, patients with a diagnosis of cancer, pregnant patients, and patients who received antithrombotic treatment for reasons other than venous thrombosis. These patients were also treated as censored. Cox proportional hazards models were used to analyze the crude and adjusted effects (adjusted for age, sex, factor V Leiden levels, prothrombin G20210A mutation, high factor VIII level, and type of initial venous thromboembolic event) of excess body weight on the risk of recurrence. The proportional hazards assumption was verified by testing interactions of covariates with the log of time to recurrence. Furthermore, we evaluated any interactions of excess body weight, sex, and age. For these calculations, we used SPSS software, version 12.0 (SPSS Inc, Chicago, Illinois).

The linearity of the effect of BMI on the risk of recurrence was assessed by nonparametric modeling of the effect of BMI using restricted cubic splines and graphically and statistically comparing the results from nonparametric and linear modeling (Figure 1). While linear modeling involves estimation of only 1 Cox regression parameter corresponding to BMI, restricted cubic spline modeling estimates 2 additional parameters to allow for a nonlinear relationship between BMI and risk of recurrence. Presence of a nonlinear effect is indicated if the additional parameters are significantly different from 0.

The risk fraction attributable to overweight (population attributable risk) was computed using the pARtial package of R (available at www.r-project.org). To compute this number, and for all comparisons of characteristics between the patient group with recurrence of venous thromboembolism and the patient group without recurrence, only data from 791 patients with at least 4 years of follow-up were used, and the groups were defined by recurrence within 4 years of follow-up (yes/no). Two-sided P values lower than 5% were considered as indicating statistical significance.

**RESULTS**

**PATIENTS**

Characteristics of the 1107 patients are summarized in Table 1. The average age was 49 years, and 589 patients were women (53%). After their first venous thromboembolism, patients had received anticoagulation treatment for an average of 8 months. A total of 307 patients were carriers of the factor V Leiden mutation (28%), and the G20210A mutation in the factor II gene was found in 70 patients (6%). The average follow-up was 46 months. A total of 295 patients were excluded during follow-up for the following reasons: death (n=15, 3 due to pulmonary embolism), antithrombotic treatment for reasons other than venous thrombosis (n=180), cancer (n=22), pregnancy (n=50), and loss to follow-up (n=25). Patients were observed until death or exclusion when data were censored.

**RECURRENT OF VENOUS THROMBOEMBOLISM**

Symptomatic recurrent venous thromboembolism was seen in 168 of 1107 patients (deep vein thrombosis in 100 patients and pulmonary embolism in 68 patients). Three of the patients with pulmonary embolism died of the embolism. In 151 patients, venous thromboembolism recurred spontaneously; in 17 patients recurrence was provoked by surgery or trauma. A recurrence was experienced by 21% of men but 8% of women (P < 0.001). Patients with and without recurrence were similar in mean (SD) age: 51 (15) years vs 48 (16) years (P = 0.10). There were no significant differences between patients with and without recurrence regarding prevalence of factor V Leiden (36% vs 28%) (P = 0.08) and duration of anticoagulation (median/75th percentile, 6.6/9.1 months vs 6.5/7.5 months) (P = 0.08). No difference was found with respect to the distribution of factor II G20210A (10% and 7%) (P = 0.20).

**Table 1. Baseline Characteristics of the 1107 Patients**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at first venous thromboembolism, mean (SD), y</td>
<td>49 (16)</td>
</tr>
<tr>
<td>Men, No.</td>
<td>518</td>
</tr>
<tr>
<td>Women, No.</td>
<td>589</td>
</tr>
<tr>
<td>Site of thromboembolism, No. (%)</td>
<td></td>
</tr>
<tr>
<td>Proximal veins of the leg</td>
<td>388 (35)</td>
</tr>
<tr>
<td>Distal veins of the leg</td>
<td>194 (18)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>525 (47)</td>
</tr>
<tr>
<td>BMI, No. (%)</td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>416 (38)</td>
</tr>
<tr>
<td>25-29</td>
<td>420 (38)</td>
</tr>
<tr>
<td>≥30</td>
<td>271 (24)</td>
</tr>
<tr>
<td>Duration of anticoagulation, median (25th, 75th percentiles), mo</td>
<td>7 (6, 8)</td>
</tr>
<tr>
<td>Observation time, median (25th, 75th percentiles), mo</td>
<td>44 (20, 75)</td>
</tr>
</tbody>
</table>

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

**Figure 1. Age- and sex-adjusted hazard ratios for recurrent venous thromboembolism corresponding to different body mass indexes (BMIs) (calculated as weight in kilograms divided by height in meters squared). The good agreement of the nonparametric estimation and the linear approximation indicates a linear relationship between BMI and risk of recurrent venous thromboembolism throughout all levels of BMI.**
RECURRENT OF VENOUS THROMBOEMBOLISM AND BMI

Mean (SD) BMI was significantly higher in patients with recurrence than in those without recurrence: 28.5 (6.0) vs 26.9 (5.0) (P = .01). When BMI was entered as a continuous variable in a Cox proportional hazards model, the hazard ratio of recurrence was 1.051 (95% confidence interval [CI], 1.024-1.079) (P < .001) for each 1-point increase in BMI. The hazard ratio was 1.044 (95% CI, 1.013-1.076) (P = .005) after adjustment for age, sex, factor V Leiden, prothrombin G20210A mutation, high factor VIII level, and type of initial venous thromboembolic event. The relationship between excess body weight and recurrent thrombosis was linear, as revealed by the comparison of nonparametric and linear estimation of the effect of BMI on the risk of recurrence (Figure 1). Nonlinear modeling did not significantly improve the model fit compared with linear modeling (P = .81).

We next investigated the risk of recurrent thrombosis among normal weight, overweight, and obese patients (BMI <25, 25-29, and ≥30, respectively). A significant difference between the cumulative probability of recurrence was found among patients with normal weight compared with those who were overweight or obese (P = .01 by the log-rank test) (Figure 2). According to Kaplan-Meyer analysis, the probability of recurrence at 4 years was 9.3% (95% CI, 6.0%-12.7%) among patients of normal weight and 16.7% (95% CI, 11.0%-22.3%) and 17.5% (95% CI, 13.0%-22.0%) among patients who were overweight and obese, respectively. Compared with patients of normal weight, the adjusted hazard ratio of recurrence was 1.3 for overweight patients (95% CI, 0.9-1.9) (P = .20) and 1.6 for obese patients (95% CI, 1.1-2.4) (P = .02) (Table 2).

Patients with excess body weight were older, had increasingly high levels of clotting factors and C-reactive protein, and were predominantly men (Table 3).

Analysis of interactions revealed that the hazard ratio corresponding to excess body weight was indepen
dent of time of recurrence, age, or sex. We were interested to know how much of the recurrence risk could be eliminated if all of our study patients would be of normal weight, and so we calculated the population attributable fraction for excess body weight and found that risk of recurrence would be lower by 26.8% (95% CI, 5.3%-48.2%) if none of the patients were overweight or obese.

In this prospective cohort study, we found that excess body weight is a risk factor of recurrent venous thromboembolism. In patients with a first unprovoked venous thromboembolism, risk of recurrence shows an almost linear relation with increasing body weight. Obesity confers the highest risk, ultimately resulting in an almost 2-fold increased risk of recurrence among patients with a BMI of 40. Compared with patients of normal weight, risk of recurrence was 30% higher among overweight patients and 60% higher among obese patients. Notably, the effect of excess body weight on risk of recurrence was independent of age and sex.

For assessing the relevance of a risk factor, both the severity and the frequency among affected individuals are important. A major finding of our study is that excess body weight was highly prevalent among patients with thrombosis; approximately 60% of these patients were overweight or obese. We assessed the contribution of excess body weight to the recurrence risk in our cohort by calculating the population attributable fraction, which was 27%.27 This finding translates into a risk reduction by more than one-quarter, assuming that all patients in our cohort were of normal weight.

The mechanisms by which excess body weight is associated with venous thrombosis are not completely understood. Obesity is thought to predispose to venous stasis, which is a trigger of deep vein thrombosis. Excess body weight has also been related to various alterations in the coagulation system, including impaired fibrinolytic activity and elevated plasma concentrations of clotting factors.28 Our findings support this notion in that levels of D-dimer, fibrinogen, factor VIII, and factor IX significantly increased according to categories of BMI. In addition, overweight and obese patients had higher levels of C-reactive protein, which indicates low-grade systemic inflammation. This observation is in agreement with the concept of the release of proinflammatory media-

![Figure 2. Kaplan-Meier estimates of the risk of recurrent venous thromboembolism in patients according to categories of body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared).](https://archinte.jamanetwork.com/)

<table>
<thead>
<tr>
<th>Body Weight Category</th>
<th>Patients/Events, No.</th>
<th>Unadjusted Relative Risk (95% CI)</th>
<th>Adjusted Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal weight</td>
<td>416/44</td>
<td>1 (Reference)</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>Overweight</td>
<td>420/74</td>
<td>1.7 (1.2-2.5)</td>
<td>1.3 (0.9-1.9)</td>
</tr>
<tr>
<td>Obese</td>
<td>271/50</td>
<td>1.9 (1.2-2.8)</td>
<td>1.6 (1.0-2.4)</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

2 Adjusted for age, sex, factor V Leiden, prothrombin G20210A mutation, high factor VIII level, and type of initial venous thromboembolic event.
tions by adipose tissue causing a hypercoagulable state and thrombus formation.28

Some strengths and limitations of our study need to be addressed. To our knowledge, this study is the first to assess the association between excess body weight and risk of recurrence in a very large prospective cohort. Patients with venous thrombosis provoked by surgery, trauma, or pregnancy and patients with venous thrombosis associated with cancer were excluded. Our findings, therefore, cannot be extrapolated to these patient groups. In our Cox proportional hazards models, risk of recurrence related to overweight and obesity was independent of other factors including sex. Our group previously showed that risk of recurrent venous thromboembolism among young women is very low and is not affected by prior oral contraceptive intake.23 Studies have demonstrated that duration of anticoagulation therapy is not associated with risk of recurrence.17,24 We therefore refrained from adjusting for previous oral contraceptive intake and duration of anticoagulation. Excess body weight was assessed by BMI, which is a good estimate of body fat but not of fat distribution. Indicators of central obesity, including waist circumference or waist to hip ratio, were not recorded in our study. Body mass index was determined once at the time of study entry, and the effect of weight change throughout the follow-up period could therefore not be evaluated.

Our findings that excess body weight confers an increased risk of recurrent venous thrombosis and is very common among patients with thrombosis can be of relevance for the management of these patients. In the absence of clinical trials, patients might still reduce thrombosis risk by losing weight. Therefore, health care professionals should be encouraged to emphasize the need for weight control when counseling overweight or obese patients with thrombosis. Obesity is a chronic disorder that requires continuous care for effective management. Comprehensive guidelines to achieve and maintain a healthy weight have recently been published.29 They include behavioral interventions such as restriction of caloric intake and enhanced physical activity. In selected patients, weight loss medications might be prescribed. Most important is ongoing medical monitoring. Since the association between excess body weight and the risk of recurrence is linear, even a small weight loss might translate into a reduction of the risk of recurrent thrombosis.

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Author Contributions: Dr Eichinger had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Eichinger, Minar, Heinze, and Kyrle. Acquisition of data: Eichinger, Bialonczyk, Hirschl, Minar, and Heinze. Analysis and interpretation of data: Eichinger, Hron, Minar, Wagner, and Heinze. Drafting of the manuscript: Eichinger. Critical revision of the manuscript for important intellectual content: Eichinger, Minar, Wagner, and Heinze. Obtained funding: Eichinger. Administrative, technical, and material support: Bialonczyk, Hirschl, Minar, and Heinze. Study supervision: Minar, Heinze, and Kyrle.

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