Idiopathic Venous Thrombosis is Associated with Preclinical Atherosclerosis

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Aim: There is growing evidence that venous thrombotic and arterial atherosclerotic diseases are interrelated. This presumption is supported by the similar ethiopathogenesis, risk factors and clinical appearance of the two diseases. We investigated whether the prevalence of preclinical indicators of atherosclerosis is higher in patients with spontaneous venous thrombosis than in healthy subjects. Further, we studied the extent of preclinical deterioration of the arterial wall in different beds of the arterial system.

Methods: Forty seven patients of both sexes (mean age, 52.3 ± 14.3 years) with idiopathic venous thrombosis and 44-age matched controls were studied. Using ultrasound, bifurcations of the carotid and femoral arteries were investigated and intima-media thickness plus the presence and thickness of atherosclerotic plaques were determined.

Results: The intima-media was on average, and in all beds investigated, significantly thicker in patients than in controls (0.94 mm ± 0.29 vs. 0.71 mm ± 0.15, p < 0.001). The prevalence of atherosclerotic plaques was higher in patients (33/47 vs. 15/44, p< 0.001). Furthermore, the number of plaques per individual, the number of arterial segments involved, and total plaque thickness were significantly longer in patients than in controls.

Conclusion: The findings showed a close interrelationship between idiopathic venous thrombosis and preclinical atherosclerotic changes in different arterial territories. This could mean that in patients with primary arterial or venous disease, the arterial and venous vessel walls deteriorate simultaneously, and that common local or systemic factors influence the clinical appearance of either or both diseases.


Key words: Venous thrombosis, Preclinical atherosclerosis, Intima media thickness, Atherosclerotic plaques

Introduction

Traditionally, the pathophysiology of thrombosis has been separated into venous and arterial thrombosis. The formation of arterial and venous thrombi has been explained by two distinct mechanisms influenced by different risk factors. Over the last few decades, however, this notion has been partially challenged by the accumulation of evidence suggesting an association between arterial atherothrombotic disease and idiopathic venous thrombosis (VT). Studies have indicated that patients with atherosclerosis may be at increased risk of venous thromboembolism and that thrombogenic factors are involved in the development of atherosclerosis. Further, recent basic and pathomorphological studies suggest similar ethiopathogenetic mechanisms and risk factors for the two diseases. Similarities in ethiopathogenetic mechanisms are also indicated by a resemblance in the appearance of atherosclerotic disease and venous thromboembolism. Grady and colleagues found the risk of venous thromboembolism in women with myocardial infarc-
tion to be 2.1-fold higher over the entire course of follow-up, but more than 5-fold higher during the first 90 days\(^9\). Further, a case control study revealed an association between venous thromboembolic disorder and arterial disease of the lower limbs\(^9\).

Atherosclerosis can be diagnosed in its preclinical phases using non-invasive imaging modalities. Several new technologies enable the visualization of early morphological deterioration of the arterial wall in atherogenesis, such as B-mode ultrasound measurements of intima-media thickness (IMT). Multiple studies have demonstrated that carotid IMT is a strong and independent predictor of cardiovascular events. In a meta-analysis of eight population-based studies, Lorenz et al. showed that every 0.1-mm increase in IMT in the common carotid artery increases the age, gender and risk factors for atherosclerosis-adjusted risk of myocardial infarction by 10% and stroke by 13%\(^10\). Baldassare et al. found that assessment of the maximum IMT improved the prediction of risk based on the Framingham risk score categories\(^11\). Further, the presence of carotid and femoral plaques, as well as total plaque thickness, were shown to be the strongest predictors of cardiovascular events\(^12\).

Several researchers believe that venous and arterial thrombosis to be a continuous spectrum of the same disease\(^15\). However, there is no consensus on whether this association exists only for clinically manifested disease or the risk for VT is related also to preclinical forms of atherosclerosis.

To test the hypothesis that a relationship exists between arterial and venous thrombosis in patients with idiopathic venous thrombosis, and that patients with preclinical atherosclerosis are at increased risk of idiopathic (spontaneous) venous thrombosis, we investigated the association between venous thrombosis and preclinical markers of atherosclerotic disease, namely intima-media thickness, and the presence of atherosclerotic plaques in the carotid and femoral arteries. Further, we studied the extent of preclinical deterioration of the arterial wall in different beds of the arterial system, considered the strongest predictor of VT among markers of atherosclerosis.

**Methods**

**Study Design and Objective**

This was a case-control study aimed at evaluating the relationship between idiopathic deep venous thrombosis and preclinical markers of atherosclerosis. The protocol was approved by the National Ethics Committee and all subjects provided written informed consent.

**Patients**

Consecutive patients admitted to our hospital or its outpatient department between June 2006 and October 2008 with symptomatic first idiopathic venous thrombosis of the lower limbs were eligible for the study. Patients with secondary thrombosis or symptomatic atherosclerosis (known coronary artery disease, symptoms of angina pectoris, suffering from ischemic stroke, transient ischemic attack, or intermittent claudication) were excluded. Secondary thrombosis was defined as venous thrombosis associated with cancer, pregnancy or childbirth, any kind of trauma or fracture, immobilisation for more than one week, or oestrogen use.

All patients received conventional treatment: low-molecular-weight heparin followed by oral anticoagulant therapy.

During the study period, 47 patients were selected in the stable phases of the disease (two to four months after diagnosis). The control group consisted of 44 subjects who had no clinical evidence of venous thromboembolism or atherosclerosis.

The control subjects and all patients were evaluated for the presence of risk factors of atherosclerosis. They were screened for smoking, hypertension, obesity, diabetes mellitus, and dyslipidemia (defined as a low-density lipoprotein cholesterol concentration ≥ 3.0 mmol/L). Patients with renal disease and renal dysfunction (based on creatinine levels) were excluded. Demographic characteristics including age, sex, height and body mass index (BMI) were recorded for all participants.

**Ultrasonographic Investigation of the Carotid and Femoral Arteries**

Bilateral assessments of the carotid and femoral arteries were performed by a trained operator. A commercially available GE Vivid 3 Expert machine (General Electric Ultrasound, Germany) with a 7–10 MHz probe for B-Mode imaging and for pulsed-wave and color Doppler imaging was used. Examinations were performed in a horizontal position. During the examination of the carotid arteries, the patient’s neck was rotated 45° in the direction opposite the side being examined. The carotid trunk was identified with the use of both B-mode and pulsed-wave color Doppler ultrasonography. The presence of atherosclerotic plaques was recorded and intima media thickness was measured. Bifurcations of the femoral arteries were similarly investigated.

Ultrasound examinations and measurements of IMT were performed according to the guidelines of the Mannheim Consensus\(^14\).
Measurement of Intima-Media Thickness (IMT)

On the basis of differences in tissue density in the B-scan, the layers of the arterial wall were represented as parallel echogenic bands separated by a relatively hypoechoic space (the double line pattern). IMT was defined as the distance from the leading edge of the first echogenic line to that of the second. The first line represents the lumen-intima interface, and the second line represents the collagen-containing upper layer of the adventitia. The carotid artery was scanned bilaterally in the longitudinal plane. Two angles of interrogation were used: anterolateral and lateral. The image was focused on the posterior (far) wall. The far-wall carotid IMT was visualized bilaterally at two sites: the common carotid artery (2 cm below the bifurcation) and the carotid bulb. Three measurements were obtained for each site at 5-mm intervals during the end-diastole of a single heartbeat and an average IMT was calculated for six measurements for both sides.

Further, the common femoral and superficial femoral arteries were investigated. Three IMT measurements were obtained from the common femoral artery (2 cm proximal from the bifurcation) and the superficial femoral artery (2 cm distal from the bifurcation). As for the carotid arteries, an average IMT was calculated for the femoral arteries from six measurements on both sides. A further measurement of average IMT was obtained by averaging the carotid and femoral IMT (total average IMT).

Investigation of Atherosclerotic Plaques

All accessible segments of the carotid arteries, the distal part of the common femoral arteries and the proximal segment of the femoral superficial arteries (bifurcations) were visualized and atherosclerotic lesions (plaques) were recorded. A plaque was defined as a focal structure that encroaches into the arterial lumen by 50% of the surrounding IMT value\(^{19}\). Total plaque thickness was determined as the sum of the largest thickness of all registered atherosclerotic plaques in all investigated arterial parts\(^{15}\).

Statistical Methods

The clinical and demographic characteristics of patients with symptomatic idiopathic venous thrombosis of the lower limbs and control subjects were compared using the Mann-Whitney test with continuity correction for continuous variables and Fisher’s exact test for categorical variables. Next, we fitted multivariable regression models to adjust the observed differences between patients with VT and controls for the influence of other risk factors for atherosclerosis (sex, age, presence of hypertension, of diabetes mellitus, and of dyslipidaemia, smoking and BMI; age and BMI were used as continuous variables). The adjusted analyses included the comparisons of average carotid IMT, average femoral IMT, total average IMT and total plaque thickness. These variables were log-transformed and used as response variables in four different linear regression models. A multivariable logistic model was fitted using the presence of atherosclerotic plaques as a response variable and the same covariates included in the linear models. A Wald test was used to assess the statistical significance of the covariates included in the regression models.

A Wilcoxon signed rank test with continuity correction was used to compare continuous measurements performed on the same subject and Spearman’s correlation was used to assess the correlation between two continuous variables.

All statistical tests were two-sided. \(P\)-values of 0.05 or less were considered statistically significant. Statistical analyses were performed with R statistical software\(^{16}\).

Results

Study Population

Forty seven consecutive patients with idiopathic venous thrombosis of the lower limbs were studied. During the study period, 44 eligible healthy subjects gave their consent and were enrolled. The controls were selected from among volunteers and were age matched. The clinical and demographic characteristics of patients and controls are shown in Table 1. The group of patients with idiopathic venous thrombosis was similar to the controls with regard to the preva-
Ulceration of risk factors for atherosclerosis, with the exception of body mass index (BMI) which was higher in patients \((p = 0.004)\) and smoking \((p = 0.04)\), odds ratio \((OR) = 4.1\), 95% confidence interval \((95\% CI)\) for \(OR = 0.98 - 24.76\). There were 8 \((17\%)\) patients with ilio - femoral, 21 \((45\%)\) with femoro - popliteal, 12 \((25\%)\) with popliteal, and 6 \((13\%)\) with isolated \((calf)\) venous thrombosis of the lower limbs.

**Ultrasonic Measurements**

The intima-media was significantly thicker in all segments of the carotid as well as femoral arteries in patients with idiopathic venous thrombosis than in healthy subjects \((Table 2)\).

Calculation of the average IMT of both carotid bifurcations \((CCA, \text{bulb})\) and femoral bifurcations \((CFA, \text{SFA})\) showed that patients with idiopathic VT had systematically thicker intima-media than subjects without VT \((Fig. 1 and Table 2)\). Furthermore, total plaque thickness was significantly greater in the patients than controls \((p < 0.001, \text{Fig. 2})\). The presence of VT remained significantly associated with the thickness of the intima-media and with total plaque thickness even after adjusting for classical risk factors for atherosclerosis and sex \((Table 3)\). This was shown using linear regression models for average IMT, for femoral IMT, for their mean value \((\text{total average IMT})\) and for total plaque thickness. The other covariates significantly associated with intima media thickness or total plaque thickness were age of the subjects and presence of dyslipidemia; older subjects and subjects with dyslipidemia had greater intima media thickness and total plaque thickness values. The model for total average IMT \((Table 3)\) indicated that patients with venous thrombosis had on average a \(1.26\) times thicker intima media than controls \((95\% CI = 1.15 \text{ to } 1.39\) \((\text{the comparison was made between patients and controls that had the same value for all other covariates included in the model})\). IMT was also influenced by

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**Table 2. Intima-media thickness of carotid and femoral segments**

<table>
<thead>
<tr>
<th>Location</th>
<th>Patients ((n = 48))</th>
<th>Controls ((n = 44))</th>
<th>(p^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCA r</td>
<td>0.83 ± 0.20</td>
<td>0.65 ± 0.14</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CCA l</td>
<td>0.91 ± 0.29</td>
<td>0.69 ± 0.14</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>bulb r</td>
<td>1.19 ± 0.48</td>
<td>0.87 ± 0.31</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>bulb l</td>
<td>1.19 ± 0.55</td>
<td>0.86 ± 0.25</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CFA r</td>
<td>1.23 ± 0.75</td>
<td>0.92 ± 0.42</td>
<td>0.041</td>
</tr>
<tr>
<td>CFA l</td>
<td>1.14 ± 0.57</td>
<td>0.90 ± 0.46</td>
<td>0.019</td>
</tr>
<tr>
<td>SFA r</td>
<td>0.60 ± 0.18</td>
<td>0.49 ± 0.12</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SFA l</td>
<td>0.61 ± 0.18</td>
<td>0.48 ± 0.11</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Carotid (mean CCA + bulb: r + l)</td>
<td>1.03 ± 0.30</td>
<td>0.77 ± 0.16</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Femoral (mean CFA + SFA: r + l)</td>
<td>0.90 ± 0.37</td>
<td>0.70 ± 0.24</td>
<td>0.004</td>
</tr>
<tr>
<td>Average (mean Carotid + Femoral)</td>
<td>0.94 ± 0.29</td>
<td>0.71 ± 0.15</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

All values are means ± standard deviations. The unit of measurement is millimeters.

Abbreviations: CCA = common carotid artery; CFA = common femoral artery; SFA = superficial femoral artery; r = right; l = left.

\* \(p\)-value obtained from the Mann-Whitney test with continuity correction.
age: mean intima media thickness increased on average 1.12 times every 10 years (95% CI = 1.08 to 1.16).

The patients had a significantly higher prevalence of atherosclerotic plaques (at least one plaque observed in 33 of 47 patients versus 15 of 44 controls, \( p < 0.001 \), OR = 4.47, 95% CI = 1.73 to 12.14) (Fig. 3). The multivariable logistic regression model showed that the presence of venous thrombosis maintained a significant association with the presence of atherosclerotic plaques after adjustments for the risk factors of atherosclerosis (OR = 5.31, 95% CI = 1.73 to 16.32); the only other covariate significantly associated with the presence of plaques was age. Older patients had a higher probability of plaques (OR for two subjects with 10 years difference in age = 1.95, 95% CI = 1.24 to 3.07). In addition, the number of plaques and the number of carotid segments involved in individual subjects were greater among the \( p < 0.001 \), mean number of plaques for patients = 2.11, for controls = 0.66, Fig. 3).

The carotid and femoral IMT values were linearly associated, both in patients (Spearman’s correlations \( r = 0.767, p < 0.001 \)) and in controls (\( r = 0.743, p < 0.001 \)). However, median carotid IMT differed significantly from median femoral IMT (0.88 vs 0.69 mm, \( p < 0.001 \)). Moreover, the carotid intima media was thicker than the femoral intima media only in subjects whose total average IMT value was small (carotid + femoral).

### Discussion

There is evidence of an association between atherosclerotic disease and venous thrombosis. This presumption is based on the relationship between manifest atherosclerotic disease and venous thromboembolism.\(^3,17\). Common risk factors for both diseases were identified\(^{18-22}\) and one study indicated that patients with venous thromboembolism have a higher prevalence of preclinical atherosclerotic lesions than healthy subjects.\(^3\). Hence, evidence points towards extensive cross-talk between atherothrombosis and venous thromboembolism, with inflammation likely to be the basic pathogenetic process leading to the activation of coagulation in both diseases.\(^23\).

In the present study, we have shown that idiopathic VT is associated with morphological preclinical

### Table 3. Linear regression for study characteristics (response variables were log transformed)

<table>
<thead>
<tr>
<th>Variable</th>
<th>IMT of carotid arteries</th>
<th>IMT of femoral arteries</th>
<th>Mean for Carotid and femoral arteries</th>
<th>Total plaque thickness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-0.820 ( p &lt; 0.001 )</td>
<td>-0.856 ( p &lt; 0.001 )</td>
<td>-0.823 ( p &lt; 0.001 )</td>
<td>1.231 ( p &lt; 0.001 )</td>
</tr>
<tr>
<td>Age</td>
<td>0.011 ( p &lt; 0.001 )</td>
<td>0.015 ( p &lt; 0.001 )</td>
<td>0.012 ( p &lt; 0.001 )</td>
<td>0.013 ( p &lt; 0.001 )</td>
</tr>
<tr>
<td>Sex</td>
<td>-0.063 ( p = 0.15 )</td>
<td>-0.090 ( p = 0.17 )</td>
<td>-0.064 ( p = 0.15 )</td>
<td>-0.07 ( p = 0.14 )</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.034 ( p = 0.50 )</td>
<td>0.080 ( p = 0.29 )</td>
<td>0.063 ( p = 0.23 )</td>
<td>0.06 ( p = 0.28 )</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>-0.086 ( p = 0.31 )</td>
<td>-0.142 ( p = 0.27 )</td>
<td>-0.08 ( p = 0.37 )</td>
<td>-0.12 ( p = 0.22 )</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>0.122 ( p = 0.02 )</td>
<td>0.171 ( p = 0.18 )</td>
<td>0.14 ( p = 0.01 )</td>
<td>0.15 ( p = 0.008 )</td>
</tr>
<tr>
<td>Smoking</td>
<td>-0.005 ( p = 0.93 )</td>
<td>0.096 ( p = 0.30 )</td>
<td>0.05 ( p = 0.45 )</td>
<td>0.05 ( p = 0.48 )</td>
</tr>
<tr>
<td>BMI</td>
<td>0.009 ( p = 0.09 )</td>
<td>-0.006 ( p = 0.47 )</td>
<td>0.003 ( p = 0.59 )</td>
<td>0.003 ( p = 0.64 )</td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>0.250 ( p &lt; 0.001 )</td>
<td>0.204 ( p = 0.003 )</td>
<td>0.233 ( p &lt; 0.001 )</td>
<td>0.23 ( p &lt; 0.001 )</td>
</tr>
</tbody>
</table>

Abbreviations: BMI = body mass index

Reference category is Male for Sex and Absence of condition for the other categorical covariates. Estimated coefficients and \( p \)-values (\( P \)- obtained using Wald test) for each covariate included in the multivariable model are shown.
markers of atherosclerosis. As in the study by Prandoni and colleagues\textsuperscript{3}, the prevalence of most classical risk factors for atherosclerosis in patients with idiopathic venous thrombosis was not significantly different from that in healthy subjects, with the exception of body mass index (BMI) and smoking. In the Nurses Health Study (NHS), where risk factors for pulmonary embolism in women were investigated, an increased BMI was shown to elevate the risk of pulmonary embolism and venous thrombosis\textsuperscript{19}. Increased body weight, also characterized by a higher BMI, probably promotes the formation of thrombi through different mechanisms\textsuperscript{24}. Body mass index can also be used as a surrogate for waist circumference as a basic criterium for metabolic syndrome (MetSyn)\textsuperscript{25}. Therefore in patients with idiopathic VT, insulin resistance as a basic mechanism of MetSyn could also be expected. However, insulin resistance was not investigated in our study, and to our knowledge, there is not enough evidence-based data about the impact of insulin resistance on VT. But as MetSyn has been recognised as a predictor of coronary artery disease\textsuperscript{20}, subjects with MetSyn or increased BMI (as one of the components of MetSyn) should have a higher prevalence of preclinical atherosclerotic lesions. However, in our study, BMI was not related to the presence of preclinical atherosclerotic lesions of the arterial wall, and the presence of VT was the strongest, and an independent, predictor of these lesions. Similarly, the Japanese group did not find any relationship between visceral obesity as a component of MetSyn and IMT\textsuperscript{27}.

The NHS study also found smoking, hyperlipidemia and hypertension to be associated with a greater likelihood of pulmonary embolism\textsuperscript{19}. Older age, a well known risk factor for atherosclerosis, has long been recognized as an independent risk factor for venous thrombosis and atherosclerosis\textsuperscript{20}.

It is not clear whether gender influences the prevalence of first idiopathic VT. In most studies, the incidence of VT was approximately equal in males and females, but the Leiden Thrombophilia Study (LTS) found a higher prevalence of males and in some studies there was a higher recurrence rate of idiopathic VT in males than in females\textsuperscript{28, 29}. In our study, there were more males than females with idiopathic VT. This is most probably the consequence of the inclusion crite-
ria and the definition of idiopathic VT. We used very strict criteria for idiopathic VT and excluded all females on oestrogen treatment, which was not the case in some other studies. Further, seasonal variation in the incidence of idiopathic VT among males with a peak in the autumn could have had an influence on the gender structure of our study group. Namely, the majority of our patients were recruited in autumn. This could also partially explain the higher prevalence of male patients in our study. However, in spite of the higher prevalence of males in our study, the multivariate analysis excluded any significant influence of gender on preclinical atherosclerotic lesions (IMT and total plaque thickness) (Table 3).

Therefore, the results of our study indicate that, independently of classical risk factors for atherosclerosis, in both sexes of patients with idiopathic VT, the prevalence of morphological deterioration of the arterial wall is higher and probably related to other non-classical risk factors like systemic inflammation, coagulation and platelet activation, which may play a role in stimulation of the development of both diseases. Bilora and co-workers did not find any relationship between the presence of preclinical atherosclerotic lesions and venous thrombosis in patients with secondary VT, which could mean that only patients with idiopathic VT are at increased risk of atherosclerosis and that in secondary VT, other external risk factors have a crucial role in its development.

Previous studies have shown an association between clinically manifested atherosclerotic disease and venous thrombosis, however few have examined the presence of preclinical atherosclerotic lesions in patients with VT. Our study demonstrates a relationship between asymptomatic atherosclerotic lesions and idiopathic venous thrombosis of the lower limbs. A relationship between preclinical atherosclerosis and VT was shown previously in one arterial bed, whereas in the present study, different indicators of deterioration of the arterial wall were found in different beds. Patients with idiopathic venous thrombosis had significantly thicker intima media in all segments of the carotid and femoral arteries than did healthy controls. The results also showed a close interrelationship in intima media thickening in carotid and femoral beds.

These findings indicate a systemic morphological (atherosclerotic) deterioration of the arterial wall in patients with venous thrombosis. Further, the prevalence of carotid plaques was significantly higher in patients than in controls (70% vs 34%). This association was still present after an adjustment for risk factors for atherosclerosis. In addition, the number of plaques and the number of carotid segments involved were greater among patients with spontaneous VT than controls. Moreover, total plaque thickness, one of the most reliable indicators of cardiovascular risk, was significantly higher in patients than in healthy subjects. The presence of venous thrombosis remained an independent indicator of preclinical markers of atherosclerosis (intima media thickness, total plaque thickness and number of plaques), also after an adjustment for classical risk factors of atherosclerosis.

In conclusion, these findings indicate a close interrelationship between arterial atherosclerotic and venous thrombotic disease. This could mean that in patients with primary arterial or venous disease, the arterial and venous vessel walls deteriorate simultaneously and that additional local or systemic factors influence the clinical appearance of either or both diseases.

Disclosure of Conflict of Interests

no conflict of interest.

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