HYPERHOMOCYSTEINEMIA AS A RISK FACTOR FOR DEEP-VEIN THROMBOSIS

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Abstract
Background. Previous studies have suggested that hyperhomocysteinemia may be a risk factor for venous thrombosis. To assess the risk of venous thrombosis associated with hyperhomocysteinemia, we studied plasma homocysteine levels in patients with a first episode of deep-vein thrombosis and in normal control subjects.

Methods. We measured plasma homocysteine levels in 269 patients with a first, objectively diagnosed episode of deep-vein thrombosis and in 269 healthy controls matched to the patients according to age and sex. Hyperhomocysteinemia was defined as a plasma homocysteine level above the 95th percentile in the control group (18.5 μmol per liter).

Results. Of the 269 patients, 28 (10 percent) had plasma homocysteine levels above the 95th percentile for the controls, as compared with 13 of 103 controls (matched odds ratio, 2.5; 95 percent confidence interval, 1.2 to 5.2). The association between elevated homocysteine levels and venous thrombosis was stronger among women than among men and increased with age. The exclusion of subjects with other established risk factors for thrombosis (e.g., a deficiency of protein C, protein S, or antithrombin; resistance to activated protein C; pregnancy or recent childbirth; or oral-contraceptive use) did not materially affect the risk estimates.

Conclusions. High plasma homocysteine levels are a risk factor for deep-vein thrombosis in the general population.

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RESULTS

The ratio of male to female subjects among both the case patients and the controls was 1.1:3, and the mean age was 44 years (range, 16 to 70 for the case patients and 16 to 71 for the controls); both these variables were used in matching the case patients and the controls.

The median plasma homocysteine level in the patients was 12.9 μmol per liter (range, 4.8 to 60.2), and that in the controls was 12.3 μmol per liter (range, 6.4 to 37.5). The homocysteine concentrations of individual case patients and controls are shown in Figure 1.

![Figure 1. Plasma Homocysteine Levels in 269 Patients with Deep-Vein Thrombosis and 269 Controls. Values shown have been rounded.](image-url)

The 95th percentile of the homocysteine levels in the control group was 18.5 μmol per liter. Of the 269 patients, 28 (10 percent) exceeded this cutoff, as compared with 13 (5 percent, by definition) in the control group. The matched odds ratio for deep-vein thrombosis in subjects with a homocysteine concentration above the 95th percentile, as compared with those whose homocysteine levels were at or below that value, was 2.5 (95 percent confidence interval, 1.2 to 5.2). When the cutoff was set at the 90th percentile, the matched odds ratio was 1.9 (95 percent confidence interval, 1.1 to 3.3); it was 4.0 (95 percent confidence interval, 1.4 to 12.0) when the cutoff was the 75th percentile (Table 1).

In order to evaluate the possibility of a dose–response relation, we stratified the patients and controls according to their homocysteine concentrations and calculated odds ratios for thrombosis in the patients at the higher levels as compared with those at the lowest level. As Figure 2 shows, the risk of thrombosis did not increase among subjects with homocysteine levels up to 18 μmol per liter; the risk was greatly increased above 22 μmol per liter, however, indicating a threshold effect rather than a continuous dose–response relation.

Odds ratios for several age groups and for men and women separately are shown in Table 2. For both sexes, there was a sharp increase in the risk of thrombosis associated with hyperhomocysteinemia at increasing ages. The overall odds ratio for thrombosis associated with hyperhomocysteinemia in women was 7.0 (95 percent confidence interval, 1.6 to 30.8), and in men it was 1.4 (95 percent confidence interval, 0.6 to 3.4), with the cutoff set at the 95th percentile of the homocysteine levels in the control group (P = 0.067 for the comparison between the sexes). When we calculated the 95th percentile of the distribution of homocysteine levels for men and women separately, we found a 95th percentile of 17.1 μmol per liter among women and 20.0 μmol per liter among men in the control group. Using these cutoffs for hyperhomocysteinemia, we found an odds ratio for thrombosis of 3.8 (95 percent confidence interval, 1.4 to 10.2) for women and 1.8 (95 percent confidence interval, 0.6 to 5.4) for men.

The higher rate of hyperhomocysteinemia in women than in men was present at all ages, making it unlikely that the difference was due to risk factors specific to women, such as the use of oral contraceptives, recent childbirth, or pregnancy. Indeed, when we excluded women with these risk factors, the unmatched odds ratio for thrombosis that was associated with hyperhomocysteinemia (with the 95th percentile for both sexes — 18.5 μmol per liter — as the cutoff for hyperhomocysteinemia) among women under the age of 50 was 11.3 (95 percent confidence interval, 2.7 to 46.0), whereas it was 2.8 (95 percent confidence interval, 0.9 to 8.7) for all women, both those with and those without these risk factors, under the age of 50.

Of the 269 patients, 15 had protein C deficiency, 7 had protein S deficiency, and 10 had antithrombin deficiency. In the control group, four had protein C deficiency,
Table 1. Pairwise Distribution of Plasma Homocysteine Values in 269 Case Patients and Their Matched Controls, According to Various Definitions of Hyperhomocysteinemia.1

<table>
<thead>
<tr>
<th>Cutpoint</th>
<th>Cases</th>
<th>Controls</th>
<th>Matched odds ratio for thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below cutoff</td>
<td>6 pairs</td>
<td>38 pairs</td>
<td>1.9 (95% CI, 1.1–3.3)</td>
</tr>
<tr>
<td>Below cutoff</td>
<td>20 pairs</td>
<td>205 pairs</td>
<td>2.0 (95% CI, 1.2–5.2)</td>
</tr>
<tr>
<td>Matched odds ratio for thrombosis, 2.5 (95% CI, 1.2–5.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below cutoff</td>
<td>3 pairs</td>
<td>25 pairs</td>
<td>4.0 (95% CI, 1.4–12.0)</td>
</tr>
<tr>
<td>Below cutoff</td>
<td>10 pairs</td>
<td>231 pairs</td>
<td>2.5 (95% CI, 1.2–5.2)</td>
</tr>
<tr>
<td>Matched odds ratio for thrombosis, 4.0 (95% CI, 1.4–12.0)</td>
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</table>

1For each cutpoint, subjects classified as having hyperhomocysteinemia were those with plasma homocysteine levels above the cutpoint value, and subjects classified as not having hyperhomocysteinemia were those with levels at or below the cutpoint value ("below cutoff"). The percentiles used as cutpoints were for the distribution of homocysteine values in the control group. Odds ratios were calculated as the risk of thrombosis in the subjects with hyperhomocysteinemia as compared with that in the subjects without hyperhomocysteinemia. CI denotes confidence interval.

Our study shows that hyperhomocysteinemia is a risk factor for deep-vein thrombosis in the general population. Moreover, our results suggest that the association between mild hyperhomocysteinemia and venous thrombosis is similar in degree to that reported for hyperhomocysteinemia and arterial vascular disease. An unexpected finding was the substantial increase in the risk of thrombosis at the highest plasma homocysteine levels. Our data suggest that there may be a threshold level above which homocysteine has a thrombogenic effect.

Falcon et al. reported that hyperhomocysteinemia was a risk factor for juvenile thrombosis.6 Our data imply that hyperhomocysteinemia is a risk factor for thrombosis in adult subjects as well, since we found an increasing odds ratio with increasing age.

When we analyzed men and women separately, we found a difference in the risk of thrombosis associated with hyperhomocysteinemia. Even when we used different cutpoints for hyperhomocysteinemia in men and women by calculating the 95th percentiles of their homocysteine distributions in the control group separately, we found that the odds ratio was roughly twice as high for women as for men. This suggests that women may be more susceptible to the pathologic effects of elevated homocysteine levels, even though their homocysteine levels are in general lower than those of men.1 This effect cannot be explained by risk factors specific to women (such as pregnancy, recent childbirth, and oral contraceptive use); an effect of these risk factors was unlikely in any case because the difference between men and women who did not have such risk factors was even more pronounced.

Hyperhomocysteinemia remained a risk factor for

Figure 2. Odds Ratio for Thrombosis According to Plasma Homocysteine Level.

The reference category was the subjects with plasma homocysteine values of <12 μmol/liter.
with hyperhomocysteinemia, the combined effect in our cell membranes perhomocysteinemia may reflect abnormal methionine risk factor for deep-vein thrombosis in the general pop­

eral genetic alterations in enzymes involved in homocys­
tininc has a toxic effect on the vascular endothelium and
other well-established risk factors; that is, the associa­
tion with thrombosis was not explained by the presence of other hereditary risk factors for thrombosis, such as a deficiency of protein C, protein S, or antithrombin. The same was true of the most common hereditary risk fac­
tor for deep venous thrombosis, resistance to activated protein C, since hyperhomocysteinemia also increased the risk of thrombosis in those without this abnormal­
ity. We investigated a possible interaction between re­

dition interval.

The odds ratio was 12.0 (95 percent confidence interval, 1.6 to 92.3) when the cutoff used was the 90th percentile in the control group.

It remains unclear whether hyperhomocysteinemia of different caus­

Elevated homocysteine levels may result from low lev­

of folic acid, vitamin B_{12}, or vitamin B_{6}. Moreover, sev­

eral genetic alterations in enzymes involved in homocys­
tine metabolism have been described.\textsuperscript{20,22} It remains unclear whether hyperhomocysteinemia of different caus­
es entails the same risk of thrombosis. Nevertheless, it is well known that vitamin supplementation lowers homocysteine concentrations in almost all subjects with hyperhomocysteinemia, regardless of the underlying cause.

We conclude that mild hyperhomocysteinemia is a risk factor for deep-vein thrombosis in the general pop­

ulation. The next question to be answered is whether homocysteine-lowering therapy — folic acid, vitamin

B_{6}, or vitamin B_{12} — contributes to the prevention of recur­
cent venous thrombosis.\textsuperscript{23-25}

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