Rapid Communication

High Prevalence of Hyperhomocysteinemia in Patients with Inflammatory Bowel Disease: a Pathogenic Link with Thromboembolic Complications?

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Summary

Background and Aims. Why patients with inflammatory bowel disease are at increased risk for thrombosis is unknown. Since they may have impaired absorption of vitamins that regulate the metabolism of homocysteine, we tested the hypothesis that they have hyperhomocysteinemia, an established risk factor for arterial and venous thrombosis. Methods. The concentrations of total homocysteine (tHcy), folate and cobalamin were measured in blood samples from 61 consecutive patients with inflammatory bowel disease and 183 age- and sex-matched healthy controls. Results. The mean (± S.D.) concentration of plasma tHcy was higher in patients (12.2 ± 7.7 μmol/l) than in controls (10.5 ± 4.6, p = 0.045). Eight patients (13%) had concentrations of tHcy higher than the 95th percentile of distribution among controls, as compared with 9 healthy controls (5%, p = 0.04). The prevalence of folate deficiency was higher in patients (15%) than in controls (5%, p = 0.02). Oral administration of folate, cobalamin and pyridoxine to 15 patients for 30 days decreased their mean tHcy levels from 20.3 ± 9.9 to 9.5 ± 3.4 (p < 0.001). Conclusions. In patients with inflammatory bowel disease there is an increased prevalence of hyperhomocysteinemia, which can be corrected by the administration of folate, cobalamin and pyridoxine. The high prevalence of hyperhomocysteinemia may account for the thrombotic risk of IBD patients; whether or not its correction will decrease the thrombotic risk should be tested in properly designed clinical trials.

Introduction

Patients with inflammatory bowel disease (IBD) are at increased risk for thromboembolic episodes affecting both the venous and the arterial circulation and occurring with frequencies varying between 1.2% and 32% in clinical and autopsy series (1, 2). Several studies have been performed to investigate the possible mechanisms underlying the tendency towards thromboembolic episodes in IBD patients. Most of them focused on the presence of a hypercoagulable state, due to increased concentrations of procoagulant factors and/or decreased activities of natural anticoagulant and fibrinolytic proteins, or to the presence of antiphospholipid antibodies (3-10). Since the reported results have often been conflicting, no definite conclusion has been reached so far on the pathogenetic link between thrombosis and IBD, which remains unclear.

In the last two decades it has been demonstrated that high plasma levels of homocysteine are associated with increased risk for both arterial (11-13) and venous (14-19) thrombosis. Homocysteine is a sulfur aminoacid derived from the metabolic conversion of methionine, whose intracellular metabolism occurs through enzymatic pathways dependent on vitamins as cofactors (12, 13). Increased plasma levels of homocysteine may be due to inherited abnormalities of enzymes involved in its metabolism or to acquired deficiencies of their cofactors, such as folate, cobalamin or pyridoxine (12, 13). The importance of vitamins as determinants of plasma homocysteine has been documented in epidemiological studies which have shown that in apparently healthy individuals there are significant negative correlations between homocysteine concentrations and serum levels and daily intakes of folate and cobalamin (20, 21). Since patients with IBD may have impaired absorption of folate (22-24), cobalamin and perhaps other vitamins, in this case-control study we compared the plasma levels of homocysteine in patients with IBD to those in healthy controls.

Methods

Two groups of subjects were studied. 1. IBD patients: 61 patients with IBD (M/F: 29/32, median age 40y, range 19-76), of whom 29 had ulcerative colitis (UC) and 32 had Crohn’s disease (CD). They were seen consecutively at our outpatient clinic between October 1995 and October 1996 to be screened for gastrointestinal diseases or to undergo regular follow-up visits. Twenty-six of them (14 with UC and 12 with CD) had active disease; 46 were treated with 5-aminosalycylic acid, 4 with salicylazosulfapyridine (SASP), 8 with azathioprine and 2 with steroids. Sixteen additional patients had been previously treated with SASP, which had been interrupted between 6 months and 8 years before enrollment in the study. 2. Healthy controls: 183 apparently healthy subjects (M/F: 87/96, median age 40 y, range 17-79), who were from the same geographical area and had the same social background as the study population. None of the subjects studied had had previous episodes of venous thromboembolism or arterial occlusive disease. All subjects granted their informed consent to the study.

Blood samples were taken from fasting individuals between 8:00 and 9:00 am for routine laboratory tests (including blood cell count, creatinine, cholesterol, triglycerides, liver function tests) and for measurements of plasma total...
Table 1  Concentrations of plasma tHcy and serum folate and cobalamin in the three study groups

<table>
<thead>
<tr>
<th></th>
<th>Healthy controls (n = 183)</th>
<th>IBD patients (n = 61)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>tHcy (µmol/L)</td>
<td>10.5 ± 4.6</td>
<td>12.2 ± 7.7</td>
<td>0.045</td>
</tr>
<tr>
<td>Folate (ng/mL)</td>
<td>6.3 ± 2.6</td>
<td>5.8 ± 4.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Cobalamin (ng/mL)</td>
<td>0.4 ± 0.2</td>
<td>0.5 ± 0.4</td>
<td>0.1</td>
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</tbody>
</table>

Means ± S.D.

Discussion

This controlled study shows that the prevalence of hyperhomocysteinemia is higher for patients with IBD than for healthy controls. Hyperhomocysteinemia in IBD patients was associated with low serum levels of folate and/or cobalamin. Since folate and cobalamin are essential cofactors in the remethylation of homocysteine to methionine, the association of their deficiency with hyperhomocysteinemia is likely to be causal. This hypothesis is supported by our observation that the daily administration of folate, cobalamin and pyridoxine to IBD patients for 30 days corrected the metabolic abnormalities in most of them (26). Although the serum levels of pyridoxine were not measured, it is likely that they were low in IBD patients, since individuals with a deficiency of other members of the B complex may also have a relative deficiency of pyridoxine (27). As a matter of fact, suboptimal pyridoxine levels have been found in apparently healthy men with hyperhomocysteinemia and deficiencies of folate and cobalamin (28). For the above reasons, pyridoxine was also given to IBD patients to favour the metabolic conversion of homocysteine to cysteine through the trans-sulfuration pathway, in which pyridoxine acts as the main cofactor.

The suboptimal vitamin status found in IBD patients could be due to a combination of several factors. An altered intracellular cobalamin status has been hypothesized in Crohn’s disease (29). Inadequate dietary intake may certainly be present in patients with severe disease, who refrain from eating in order to mitigate the symptoms of the disease. In addition, increased utilization, particularly of folate, may be observed...
in patients with active inflammatory disease (22). The third factor in the pathogenesis of vitamin deficiency in IBD could be malabsorption due to involvement of the dedicated regions of the intestinal mucosa or to the presence of chronic diarrhea or other intestinal dysfunctions (30).

For instance, impaired absorption of folate has been documented not only in patients with Crohn’s disease involving the jejunum, but also in those in whom the lower ileum was affected (22). This finding may be interpreted to indicate that abnormalities of the ileum might also affect jejunal function (22) or that microscopic involvement of the jejunum can affect its function. Another factor implicated in the malabsorption of folate in IBD is treatment with SASP (23, 24), which has certain properties of an antifolate drug (31, 32). In our study we did find that the prevalence of folate deficiency in IBD patients who were or had been on treatment with salicylazosulfapyridine was higher than in IBD patients on other types of treatment. However, prevalences of cobalamin deficiency and of hyperhomocysteinemia were similar in these two subgroups of IBD patients, indicating that the causes of vitamin deficiency and, consequently, of hyperhomocysteinemia in IBD can not only be attributed to the antifolate effects of SASP.

Our observation of a high prevalence of hyperhomocysteinemia in IBD patients can at last shed some light on the pathogenic link between IBD and thrombosis. To our knowledge, since the demonstration that IBD patients are at high risk for both arterial and venous thrombosis (reviewed in ref. 1), this is the first study clearly showing that the prevalence of an established risk factor for both arterial and venous thrombosis, such as hyperhomocysteinemia (11-19), is high in patients with IBD. By definition, risk factors for a disease identify subjects at risk of the disease. Therefore, the high prevalence of hyperhomocysteinemia that we found in our study can account for the high risk of thrombosis of IBD patients. The fact that none of our patients had previous thrombotic complications is not in contrast with this conclusion. Since thrombosis is a multifactorial disease, the likelihood of developing thrombotic manifestations increases with the number of risk factors present in a given individual. It is likely, therefore, that high tHcy levels predispose IBD patients to thrombotic episodes, which are precipitated by the coexistence of other circumstantial or permanent risk factors. Among the latter, increased titers of anticardiolipin antibodies (5, 9) and hypercoagulable states due to either increased plasma concentrations of procoagulant factors or to decreased levels of naturally occurring anticoagulants or profibrinolytic factors have been occasionally described in some studies (4, 6), but not in others (5, 10).

In conclusion, our study indicates that hyperhomocysteinemia and vitamin deficiencies are common findings in IBD patients and may expose them to an increased risk for thrombotic episodes. In addition, it indicates that, due to the high prevalence of these abnormalities, an accurate assessment of the nutritional status of IBD patients and, when indicated, the correction of vitamin deficiencies are warranted. Whether or not this therapeutic approach will also decrease the thrombotic risk of IBD patients should be tested in properly designed clinical trials.

References


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