Low Circulating Folate and Vitamin B₆ Concentrations Risk Factors for Stroke, Peripheral Vascular Disease, and Coronary Artery Disease

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Background—A high plasma homocysteine concentration is a risk factor for atherosclerosis, and circulating concentrations of homocysteine are related to levels of folate and vitamin B₆. This study was performed to explore the interrelationships between homocysteine, B vitamins, and vascular diseases and to evaluate the role of these vitamins as risk factors for atherosclerosis.

Methods—In a multicenter case-control study in Europe, 750 patients with documented vascular disease and 800 control subjects frequency-matched for age and sex were compared. Plasma levels of total homocysteine (before and after methionine loading) were determined, as were those of red cell folate, vitamin B₁₂, and vitamin B₆.

Results—In a conditional logistic regression model, homocysteine concentrations greater than the 80th percentile for control subjects either fasting (12.1 μmol/L) or after a methionine load (38.0 μmol/L) were associated with an elevated risk of vascular disease independent of all traditional risk factors. In addition, concentrations of red cell folate below the lowest 10th percentile (<513 nmol/L) and concentrations of vitamin B₆ below the lowest 20th percentile (<23.3 nmol/L) for control subjects were also associated with increased risk. This risk was independent of conventional risk factors and for folate was explained in part by increased homocysteine levels. In contrast, the relationship between vitamin B₆ and atherosclerosis was independent of homocysteine levels both before and after methionine loading.

Conclusions—Lower levels of folate and vitamin B₆ confer an increased risk of atherosclerosis. Clinical trials are now required to evaluate the effect of treatment with these vitamins in the primary and secondary prevention of vascular diseases.

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Key Words: atherosclerosis ■ cerebrovascular disorders ■ coronary disease ■ peripheral vascular disease ■ risk factors

An increased plasma homocysteine concentration is associated with premature arterial disease1–16 and may reflect deficiency states of folate, vitamin B₁₂, or vitamin B₆.17–19 or of certain essential enzymes.20–25 The relationship between these B vitamins and vascular diseases, however, remains poorly defined. The present study demonstrates that lower circulating levels of folate and vitamin B₆ are often seen in patients with atherosclerosis and confer an increased and independent risk of cardiovascular disease.

Methods

Case Subjects

Patients with clinical evidence of coronary artery disease, peripheral vascular disease, or cerebrovascular disease confirmed by standard diagnostic techniques were included. The inclusion and exclusion criteria have been reported extensively elsewhere.15 Briefly, 750 case subjects with vascular disease and 800 control subjects younger than 60 years of age, of both sexes, were recruited at 19 centers in nine European countries. Case subjects had defined clinical and objective investigational evidence of vascular disease. Newly or recently diagnosed case subjects were recruited wherever possible, and 69% were recruited within 1 year of diagnosis. Exclusion criteria for both case and control subjects included nonatherosclerotic vascular disease, cardiomyopathy, diabetes mellitus, pregnancy, recent (within 3 months) systemic illness, and psychiatric illness. Conditions thought to influence homocysteine concentrations, such as renal or thyroid

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disease, anticonvulsant therapy, and recent (<3 months) exposure to nitrous oxide, also served as exclusion criteria.

Control Subjects
Control subjects were clinically healthy and free of overt disease. Where possible, subjects were recruited from a geographic background similar to that of case subjects. Community-based control subjects from random population samples, family practice registers, and occupational registers were considered ideal sources. Just less than half of these subjects came from community samples, one third were recruited from employee health insurance registers, and one sixth were hospital employees. Two percent of control subjects were hospital patients. Control subjects recruited from the three main sources were similar in terms of the major variables studied and plasma total homocysteine (tHcy) levels.

Risk Factors for Vascular Disease
Age, sex, smoking habits, blood pressure, lipid concentrations, weight, and both drug and vitamin usage were documented in all subjects and are shown in Table 1.

Methionine-Loading Test
A methionine-loading test was performed on all subjects in standard fashion. Blood was drawn into tubes containing EDTA for measurement of fasting tHcy. An oral dose of 0.1 g/kg i-methionine was administered, and blood was drawn again 6 hours later for the postload measurement. We refer to the difference between these two concentrations as the increase in tHcy.

Laboratory Measurements

Homocysteine Assay
Total plasma homocysteine was measured by a previously described method involving reduction with sodium borohydride, derivatization with monobromobimane, high-performance liquid chromatography (HPLC) separation, and fluorescence detection. Blinded analyses were performed on all samples that were reanalyzed twice on two separate days. A maximum of 10% difference between the results was allowed. If this was exceeded, the analyses were repeated for a third time. The average of these analyses is presented.

Vitamin Concentrations and Other Assays
Measurements of red cell folate, vitamin B12, and vitamin B6 (measured as pyridoxal 5'-phosphate) and creatinine were performed centrally at Mimelab-AB, Soraker, Sweden. Vitamin B12 and folate concentrations were measured by use of a radioimmunoassay technique, and pyridoxal 5'-phosphate was measured by enzymatic photometry with HPLC separation.

Definitions

Traditional Risk Factors
Smokers were defined as those currently smoking any tobacco (at the time of diagnosis for case subjects and at the time of the methionine-loading test for control subjects). Hypertension was considered present if at the time of the methionine-loading test a systolic blood pressure $\geq 160$ mm Hg or a diastolic pressure of $95$ mm Hg was observed or if treatment for high blood pressure was administered. For both systolic and diastolic blood pressures, the mean of four values was used (two obtained before and two after the administration of methionine). Hypercholesterolemia was considered present if subjects were taking lipid-lowering drug treatment or had a serum cholesterol $\geq 6.5$ mmol/L (251.4 mg/dL).

Homocysteine Concentrations
For categorical analyses, high tHcy concentrations were defined as levels greater than the 80th percentile for control subjects in both the fasting (12 mmol/L) and the post–methionine-loading state (38 mmol/L). The 80th percentile for control subjects was also used to define an abnormally high increase after methionine loading (27 mmol/L).

Vitamin Deficiencies and Low Vitamin Status
Folate deficiency was defined as a red cell folate concentration $<372$ mmol/L, which is similar to widely used reference ranges. Low folate status was defined as a concentration below the 10th percentile for control subjects (513 mmol/L). Concentrations of fasting tHcy below this level of folate were higher than those in the upper decile of folate concentration (see Figure). Because this difference persisted when adjusted for deficiencies of both vitamin B12 and vitamin B6, we inferred a functional folate deficiency at and below this level. Vitamin B12 deficiency was defined as a plasma concentration $<125$ pmol/L. Low vitamin B12 status was defined arbitrarily as a value below the 10th percentile for control subjects (139.5 pmol/L).

Definitions of vitamin B12 deficiency are not uniform, and values $<30$ or $<20$ nmol/L may indicate deficiency. In the present study, frank deficiency was defined as $<20$ nmol/L. Because this was almost identical to the 10th percentile for control subjects (20.8 nmol/L), low vitamin B12 status was defined as less than the 20th percentile for control subjects (23.3 nmol/L).

Diagnostic Criteria for Vascular Disease
The following criteria were used for the diagnosis of vascular diseases:
1. Coronary heart disease: clinical evidence of angina or myocardial infarction plus a $\geq 2$-fold rise in cardiac enzymes with evolutionary ST-T changes or pathological Q waves alone or angiographic evidence of $\geq 70\%$ stenosis of a major coronary artery.

2. Cerebrovascular disease: clinical evidence of stroke or transient ischemic attack plus carotid stenosis $\geq 50\%$ on Doppler or angiography or unequivocal atherosclerotic plaque on angiography or computed tomographic evidence of cerebral infarction without demonstrable source of embolism.

3. Peripheral vascular disease: clinical evidence of intermittent claudication or clearly diminished foot pulses plus obstruction of one major peripheral artery on angiography or Doppler ankle-arm index, 0.9.

Statistical Methods

Sample size considerations for this study have been presented elsewhere. Data are presented as mean $\pm$ SE or percents. When necessary, log transformation was used for skewed variables, and these data are presented as geometric means and 95% CIs. We compared risk factors between case and control subjects using a $t$ test or $\chi^2$ test as appropriate. We examined the relationship among tHcy and vitamin concentrations using Pearson correlations. Conditional logistic regression stratified by center, age, and gender was used to investigate models of the risk of coronary artery disease; odds ratios with 95% CIs are reported for these analyses. Differences in tHcy among vitamin deciles were evaluated with ANOVA. A two-sided 5% level of significance is considered significant for all statistical tests; exact probability values are reported down to $P<.001$.

Results

Concentrations of tHcy

Geometric means for fasting, postload, and increase in tHcy values and for the vitamins are shown in Table 2 according to gender and case status. Overall, fasting tHcy values were higher in case subjects than in control subjects in both men and women. Age and weight adjustment had little effect on the values shown in the tables or on significance levels (data not shown). After the methionine-loading test, tHcy values were higher in case subjects than in control subjects, both in men and women. These concentrations also remained high when adjusted for age and weight (data not shown).

Vitamins

Folate concentrations were higher in men than in women. Within men as a group, however, folate levels were lower in case subjects than in control subjects (819.0 $\pm$ 1.0 versus 876.2 $\pm$ 1.0 nmol/L; $P=.005$; see Table 2). Mean vitamin $B_{12}$
concentrations were similar in both case and control subjects. Vitamin B6 concentrations were lower in case subjects than in control subjects.

**Correlations Between Vitamins and tHcy**

The correlations between tHcy and the three vitamins are shown in Table 3 and in the Figure.

Fasting tHcy correlated negatively with folate. Postload values correlated negatively with folate in male case subjects and in female control subjects. In contrast, values for the increase in tHcy did not correlate with folate. Fasting, postload, and increases in tHcy values correlated negatively with vitamin B12 (see Table 3) in both case and control subjects. The majority of these correlations were significant. Fasting, postload, and increases in tHcy values correlated negatively with vitamin B6 (see Table 3), and the majority of these correlations were significant. Across the range of vitamin B6 concentrations, postload tHcy levels were greater in case than control subjects (see Figure).

**Vitamin Deficiencies**

Prevalences of vitamin deficiencies (defined by use of conventional definitions) and values for the lower 10th and 20th percentiles are shown in Table 4. When a definition of folate deficiency of 372 nmol/L was used, folate deficiency was seen in 2% of control subjects and 4% of case subjects (P < .048).

Low folate status, corresponding to the 10th percentile for control subjects (513 nmol/L), was seen in 15% of case subjects (P < .002). Prevalences of deficiency of vitamin B12 (<125 pmol/L) and low vitamin B12 status were not different in case subjects than in control subjects. Deficiency (<20 nmol/L) was seen in 21% of case subjects (P < .001). This concentration was almost identical to the 10th percentile for control subjects (20.75 nmol/L; see Table 4). Low vitamin B6 status (less than the 20th percentile for control subjects, or 23.2 nmol/L) was seen in 35% of case subjects (P < .001).

**Relationships Between Homocysteine, Vitamins, and Vascular Disease**

Variables included in the conditional logistic regression models for vascular diseases included hypertension, smoking, hypercholesterolemia, creatinine, and the concentrations of fasting tHcy, postload tHcy, increase in tHcy, folate, vitamin B12, and vitamin B6. The results for these analyses are shown in Table 5.

**TABLE 3. Correlations Between Plasma Total Homocysteine and Vitamin Levels in Case and Control Subjects**

<table>
<thead>
<tr>
<th>Correlation</th>
<th>Case Subjects</th>
<th>Control Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>Folate vs Fasting tHcy</td>
<td>-0.320†</td>
<td>-0.251†</td>
</tr>
<tr>
<td>vs Postload tHcy</td>
<td>-0.162†</td>
<td>0.013</td>
</tr>
<tr>
<td>B12 vs Fasting tHcy</td>
<td>-0.273†</td>
<td>-0.292†</td>
</tr>
<tr>
<td>vs Postload tHcy</td>
<td>-0.160†</td>
<td>-0.149*</td>
</tr>
<tr>
<td>B6 vs Fasting tHcy</td>
<td>-0.160†</td>
<td>-0.254†</td>
</tr>
<tr>
<td>vs Postload tHcy</td>
<td>-0.111*</td>
<td>-0.254†</td>
</tr>
<tr>
<td>Increase</td>
<td>-0.064</td>
<td>-0.222†</td>
</tr>
<tr>
<td>Folate vs vitamin B12</td>
<td>0.087*</td>
<td>0.160*</td>
</tr>
<tr>
<td>Folate vs vitamin B6</td>
<td>0.005</td>
<td>0.099</td>
</tr>
<tr>
<td>Vitamin B12 vs vitamin B6</td>
<td>0.086*</td>
<td>0.164*</td>
</tr>
</tbody>
</table>

†tHcy indicates total homocysteine. All data are log transformed.
*P < .05; †P < .001.

**TABLE 4. Prevalence of Low Vitamin Status and Conventionally Defined Vitamin Deficiencies in Case and Control Subjects**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Threshold</th>
<th>Case Subjects</th>
<th>Control Subjects</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin B6</td>
<td>10th percentile (20.8 nmol/L)</td>
<td>35</td>
<td>20</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>20th percentile (23.3 nmol/L)</td>
<td>35</td>
<td>20</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Deficiency (20.0 nmol/L)</td>
<td>21</td>
<td>8</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>10th percentile (140 pmol/L)</td>
<td>12</td>
<td>10</td>
<td>.130</td>
</tr>
<tr>
<td>20th percentile (170 pmol/L)</td>
<td>28</td>
<td>20</td>
<td>.328</td>
<td></td>
</tr>
<tr>
<td>Deficiency (125 pmol/L)</td>
<td>8</td>
<td>6</td>
<td>.179</td>
<td></td>
</tr>
<tr>
<td>Red cell folate</td>
<td>10th percentile (513 nmol/L)</td>
<td>15</td>
<td>10</td>
<td>.002</td>
</tr>
<tr>
<td>20th percentile (604 nmol/L)</td>
<td>26</td>
<td>20</td>
<td>.007</td>
<td></td>
</tr>
<tr>
<td>Deficiency (372 nmol/L)</td>
<td>4</td>
<td>2</td>
<td>.048</td>
<td></td>
</tr>
</tbody>
</table>

Cutpoints defining groups are given in parentheses (see “Methods”) and are based on control data. Patients with deficiencies in vitamins other than the one being analyzed are eliminated from the analysis.

*For vitamin B6, n = 748 case subjects and 800 control subjects; for vitamin B12, n = 749 case subjects and 800 control subjects; and for red cell folate, n = 685 case subjects and 775 control subjects.
TABLE 5. Adjusted Odds Ratio of Vascular Disease in Subjects With High Total Homocysteine or Low Vitamin Levels Relative to Subjects With Normal tHcy or Vitamin Levels

<table>
<thead>
<tr>
<th>Variable</th>
<th>Additional Adjustment</th>
<th>RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>High fasting tHcy</td>
<td>···</td>
<td>1.96 (1.49–2.58)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Vitamin levels</td>
<td></td>
<td>1.69 (1.26–2.26)</td>
<td>.001</td>
</tr>
<tr>
<td>High postload tHcy</td>
<td>···</td>
<td>1.82 (1.39–2.40)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Vitamin levels</td>
<td></td>
<td>1.62 (1.2–2.16)</td>
<td>.001</td>
</tr>
<tr>
<td>High increase in tHcy</td>
<td>···</td>
<td>1.41 (1.06–1.86)</td>
<td>.017</td>
</tr>
<tr>
<td>Vitamin levels</td>
<td></td>
<td>1.28 (0.96–1.72)</td>
<td>.094</td>
</tr>
<tr>
<td>Folate &lt;10th percentile*</td>
<td>···</td>
<td>1.50 (1.03–2.20)</td>
<td>.045</td>
</tr>
<tr>
<td>Fasting tHcy</td>
<td></td>
<td>1.38 (0.93–2.03)</td>
<td>.108</td>
</tr>
<tr>
<td>Postload tHcy</td>
<td></td>
<td>1.45 (0.99–2.13)</td>
<td>.060</td>
</tr>
<tr>
<td>Increase in tHcy</td>
<td></td>
<td>1.50 (1.02–2.20)</td>
<td>.038</td>
</tr>
<tr>
<td>Vitamin levels</td>
<td></td>
<td>1.19 (0.8–1.76)</td>
<td>.392</td>
</tr>
<tr>
<td>B&lt;sub&gt;12&lt;/sub&gt; &lt;10th percentile*</td>
<td>···</td>
<td>1.09 (0.73–1.63)</td>
<td>.670</td>
</tr>
<tr>
<td>Fasting tHcy</td>
<td></td>
<td>1.16 (0.78–1.72)</td>
<td>.481</td>
</tr>
<tr>
<td>Postload tHcy</td>
<td></td>
<td>1.17 (0.79–1.73)</td>
<td>.440</td>
</tr>
<tr>
<td>Increase in tHcy</td>
<td></td>
<td>1.84 (1.39–2.42)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Vitamin levels</td>
<td></td>
<td>1.76 (1.33–2.34)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>B&lt;sub&gt;9&lt;/sub&gt; &lt;20th percentile*†</td>
<td>···</td>
<td>1.79 (1.35–2.37)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Fasting tHcy</td>
<td></td>
<td>1.81 (1.37–2.40)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Postload tHcy</td>
<td></td>
<td>1.45 (1.06–1.86)</td>
<td>.017</td>
</tr>
</tbody>
</table>

tHcy indicates total homocysteine; RR, relative risk.

Analyses are stratified by center, age, and gender. All models include hypertension, smoking status, hypercholesterolemia, and creatinine. All three vitamin levels are simultaneously included in models to adjust for their combined influence.

*Also adjusted for lower levels of the other two vitamins.
†The 20th percentile for vitamin B<sub>6</sub> levels is given here because the conventional definition of deficiency (<20 nmol/L) and the 10th percentile (20.75 nmol/L) were virtually identical. Odds ratio of vascular disease was in fact elevated at all three levels (deficient and less than the 10th and 20th percentiles).

**Discussion**

Increases in plasma concentrations of homocysteine are common in patients with stroke, coronary disease, and peripheral vascular disease and confer an independent risk of atherosclerosis. In the present study, important links between homocysteine, low vitamin concentrations, and vascular disease risk were seen. The causes of hyperhomocysteinemia in these patients are poorly understood, although reduced activity of cystathionine β-synthase or methylenetetrahydrofolate reductase, which are essential for the metabolism of homocysteine, could play a role. More importantly, however, concentrations of homocysteine rise as the levels of folate, vitamin B<sub>12</sub>, and vitamin B<sub>6</sub> fall, and high homocysteine concentrations are often seen with deficiency of these vitamins.

In this investigation, homocysteine levels were higher in men, although the postload increase was greater in case subjects, with a consequently greater value in total homocysteine level. The gender difference may be because of the fact that more homocysteine is formed in men than in women in conjunction with creatine-creatinine synthesis. It is also possible that there are gender differences in the transsulfuration and remethylation of homocysteine, with more efficient remethylation in women and more efficient transsulfuration in men. Men may therefore have a higher folate requirement. Indeed, in the present study, folate levels were lower in women than in men, and case-control differences were only apparent in men.

In the present study, homocysteine correlated negatively with all three vitamins, although the rise in homocysteine was steepest with lower vitamin levels. When a standard definition (372 nmol/L) was used, folate deficiency was not associated with an increased risk of vascular disease. Low folate status, however, was associated with an increased risk of vascular disease. This risk was reduced by the inclusion of fasting homocysteine in the model, implying that the increased risk of vascular disease accompanying lower folate levels may be explained by the higher circulating homocysteine concentrations. These findings are consistent with those of Pancharuniti et al, who showed an association between lower folate levels and angiographic evidence of ≥50% occlusion of one or more major coronary arteries in white males younger than 50 years of age. Recently, Morrison et al reported a higher 15-year coronary mortality rate in patients with lower folate concentrations. In their study, however, no data were available on homocysteine levels. Our findings are consistent with the observation that low functional levels of folate and other B vitamins, including vitamin B<sub>12</sub>, that are prevalent in the general population are also commonplace in patients with atherosclerosis. Because it is possible to lower homocysteine levels with folic acid, such treatment may reduce the risk of atherosclerosis.

Concentrations of vitamin B<sub>6</sub> were lower in case subjects than in control subjects, and deficiency was common (≥20%). These findings are unlikely to be a consequence of vascular disease because although vitamin B<sub>6</sub> levels may fall after...
myocardial infarction, concentrations return to baseline levels after 3 to 4 days. Confounding disorders associated with reduced vitamin B6 levels, such as cancer, renal disease, diabetes, or alcoholism, also could not have been responsible because such patients had been excluded from the present study. Control subjects had also been selected carefully, and values for random population control subjects were similar to those seen in control subjects recruited from other sources. The large sample size permitted the exploration of a number of models of vitamin B6 deficiency and low vitamin B6 status that confirmed the increased relative risk of vascular disease with lower vitamin B6 concentrations. Risk fell with rising vitamin B6 concentrations and was independent of traditional risk factors.

Adjustment for fasting, postload, and increase in homocysteine concentrations did not abolish this effect. High homocysteine concentrations often follow a methionine load and have been ascribed to cystathionine β-synthase deficiency. In such patients, however, deficiency of vitamin B6 may be a more satisfactory explanation, because the loading test may be abnormal in such case subjects and the gene frequency for cystathionine β-synthase deficiency is low. Other studies have also pointed to an increase in coronary artery disease risk with lower vitamin B6 concentrations.

In summary, low concentrations of folate and vitamin B6 are often associated with high homocysteine concentrations. Lower levels of both these vitamins confer an increased risk of vascular disease. This risk may be mediated through homocysteine in the case of folate but not in the case of vitamin B6. Such vitamin levels are commonplace in the population and include many individuals now thought to have vitamin concentrations in a normal range. The abnormalities may be readily reversed by folic acid either alone or in combination with vitamins B12 and B6. Intervention studies are now required to test the effects of such treatment on the primary and secondary prevention of vascular disease.

Appendix

Other Investigators in the European Concerted Action Project

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References

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