Association of Elevated Homocysteine Level and Vitamin B₁₂ Deficiency With Anemia in Older Adults

A recent article in the Archives¹ reported on the development of anemia in the Leiden 85-Plus Study. Folate deficiency and elevated serum homocysteine level were associated with anemia both at baseline and at the 5-year follow-up.¹ However, the authors did not assess associations between anemia and dietary and red blood cell folate levels. It is important to investigate these relationships because folate deficiency generally develops as a result of inadequate dietary intake, and red blood cell folate concentration is more reliable than serum level.² We therefore explored associations between anemia and elevated homocysteine level, as well as with vitamin B₁₂ and serum, red blood cell, and dietary folate deficiencies, in a representative population of older adults.

Methods. The Blue Mountains Eye Study (BMES) is a population-based cohort study of sensory loss and other health outcomes, with methods previously reported.³ During 1992 to 1994, 3654 participants 49 years and older were examined (82.4% participation). At 5-year follow-up examinations (BMES-2), 2335 surviving participants (75.1% of survivors; 543 had died) and an additional 1174 subjects were examined as a result of a repeated door-to-door census. This provided a second cross-sectional population sample of 3509 subjects. Of these, venous blood samples were collected from 3015 subjects. Of the 2335 survivors in BMES-2, 1952 (75.6% of survivors; 543 had died) and an additional 1174 subjects were examined as a result of a repeated door-to-door census. This provided a second cross-sectional population sample of 3509 subjects. Of these, venous blood samples were collected from 3015 subjects. Of the 2335 survivors in BMES-2, 1952 (75.6% of survivors; 1103 persons died) were re-examined at 10-year follow-up examinations (BMES-3).

Anemia, elevated mean corpuscular volume, elevated homocysteine level, and folate and vitamin B₁₂ deficiencies were assessed using the same definitions described by den Elzen et al.⁴ All possible confounders listed in the Leiden 85-Plus Study were adjusted for in our study, with the exception of obstructive lung disease and Parkinson disease. We adjusted for fractures overall rather than specifically for hip fracture, as in the study by den Elzen et al.

Results. Of the 3015 subjects at BMES-2, 503 subjects who used any form of vitamin B₁₂ and/or folic acid supplements were excluded, leaving 2512 subjects. Elevated serum homocysteine level and vitamin B₁₂ deficiency were both associated with anemia (Table). Both serum and red blood cell folate deficiency and dietary folate less than the recommended daily intake were not associated with anemia but were associated with elevated mean corpuscular volume.

In an adjusted logistic regression model including elevated homocysteine level and serum folate and vitamin B₁₂ deficiency, we observed an independent association between homocysteine and anemia (odds ratio, 3.78; 95% confidence interval, 2.12-6.74). At BMES-3, 21 subjects (7.0%) with elevated homocysteine levels had incident anemia (odds ratio, 2.09; 95% confidence interval, 1.01-4.30). Five-year incidence of anemia was not predicted by vitamin B₁₂ or serum folate deficiencies.

Comment. Our study confirms the findings by den Elzen et al.¹ that elevated serum homocysteine level is associated with both prevalent and incident anemia, demonstrating that the Leiden 85-Plus Study findings extend down to persons 50 years and older. However, in contrast, we found that vitamin B₁₂ deficiency rather than serum folate deficiency was associated with prevalent anemia. This is a valid finding because anemia is one of the most frequent consequences of vitamin B₁₂ deficiency, and in developed countries, anemia due to folate deficiency is uncommon.⁵,⁶ Elevated mean corpuscular volume could be considered as a preanemia stage, which our study shows is associated with all the deficiencies we examined.

We provide evidence supporting screening and treatment of vitamin B₁₂ deficiency, which may attenuate the occurrence of anemia in older adults. This contrasts with the recommendations by den Elzen et al.¹ for those 85 years and older. These conflicting results are not surprising, since a notable proportion of older anemic patients (30%-50%) are presumed to have multiple causes for their anemia.² Hence, both the Blue Mountains and Leiden 85-Plus studies demonstrate that successful treatment of nutrient-deficiency anemia depends on focusing particular attention to discerning underlying causes.

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Table. Relationship Between Anemia and Elevated MCV and Homocysteine Level and Folate and Vitamin B12 Deficiency

<table>
<thead>
<tr>
<th>Variable</th>
<th>Anemiaa</th>
<th>Age- and Sex-Adjusted OR (95% CI)</th>
<th>Multivariable-Adjusted OR (95% CI)c</th>
<th>Elevated MCVb</th>
<th>Age- and Sex-Adjusted OR (95% CI)</th>
<th>Multivariable-Adjusted OR (95% CI)c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homocysteine leveld</td>
<td>Normal</td>
<td>21 (1.2)</td>
<td>1 [Reference]</td>
<td>36 (2.1)</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
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<tr>
<td></td>
<td>Elevated</td>
<td>46 (6.3)</td>
<td>4.2 (2.4-7.3)</td>
<td>33 (4.6)</td>
<td>1.9 (1.1-3.1)</td>
<td>1.6 (0.9-2.8)</td>
</tr>
<tr>
<td>Serum folatee</td>
<td>No deficiency</td>
<td>62 (2.6)</td>
<td>1 [Reference]</td>
<td>66 (2.8)</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td></td>
<td>Deficiency</td>
<td>4 (5.6)</td>
<td>2.4 (0.8-7.0)</td>
<td>6 (8.5)</td>
<td>3.3 (1.4-8.0)</td>
<td>3.2 (1.2-8.5)</td>
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<tr>
<td>Red blood cell folatef</td>
<td>No deficiency</td>
<td>25 (2.3)</td>
<td>1 [Reference]</td>
<td>28 (2.6)</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td></td>
<td>Deficiency</td>
<td>3 (2.8)</td>
<td>1.0 (0.3-3.3)</td>
<td>7 (6.6)</td>
<td>2.5 (1.1-6.0)</td>
<td>2.5 (1.0-6.5)</td>
</tr>
<tr>
<td>Dietary folateg</td>
<td>Recommended daily intake</td>
<td>44 (3.0)</td>
<td>1 [Reference]</td>
<td>34 (2.3)</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td></td>
<td>&lt;Recommended daily intake</td>
<td>18 (2.9)</td>
<td>1.0 (0.6-1.8)</td>
<td>27 (4.3)</td>
<td>1.9 (1.1-3.2)</td>
<td>2.2 (1.3-3.8)</td>
</tr>
<tr>
<td>Vitamin B12 levelh</td>
<td>Normal</td>
<td>49 (2.3)</td>
<td>1 [Reference]</td>
<td>51 (2.4)</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td></td>
<td>Deficiency</td>
<td>17 (5.1)</td>
<td>1.9 (1.1-3.4)</td>
<td>21 (6.3)</td>
<td>2.5 (1.5-4.3)</td>
<td>2.4 (1.4-4.3)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; MCV, mean corpuscular volume; OR, odds ratio.

SI conversion factors: To convert hemoglobin to grams per liter, multiply by 10; folate to nanomoles per liter, multiply by 2.226; and vitamin B12 to picomoles per liter, multiply by 0.7378.

a Anemia was defined as hemoglobin level lower than 12 g/dL for women and lower than 13 g/dL for men.
b Elevated MCV was defined as higher than 100 µm³.
c Adjusted for age, sex, education, renal function (determined by the Cockcroft-Gault equation), and presence of 2 or more chronic conditions (ie, history of stroke, history of myocardial infarction, history of cancer, severe cognitive impairment with a Mini-Mental State Examination score <19, type 2 diabetes mellitus, fracture, and arthritis).
d Elevated serum homocysteine level was defined as higher than 13.5 µmol/L.
e Serum folate deficiency was defined as lower than 3.14 ng/mL.
f Red blood cell folate deficiency was defined as lower than 230.46 ng/mL.
g The recommended daily intake of dietary folate is 320-µg dietary folate equivalents or greater.
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1. e commends Dawood et al on their study, which found that simply giving smoking cessation counseling in the hospital, as mandated by current quality-initiative measures, does not result in smoking cessation. Factors that improved smoking cessation rates included receiving a referral to cardiac rehabilitation, the presence of a hospital-based smoking cessation program, and not experiencing depression. These findings are critical in helping to shape policy decisions regarding inpatient efforts to promote smoking cessation.

However, we are concerned with the authors’ conclusion that “socioeconomic status of the patients did not predict” smoking cessation. This finding is based on multivariable analyses that included “economic burden” as a potential predictor (defined as “reported avoiding health care owing to cost over the past year”). There is some question as to the rationale and appropriateness of this single-item measure to capture the socioeconomic status construct. While economic burden may be a proxy for low socioeconomic status, it may not be specific to low-income patients and may include patients who were not financially disadvantaged but believed that health care expenses are not a priority. Moreover, it was unclear why the multivariable analyses did not include annual income less than $10 000 (which was a significant predictor of smoking cessation in the bivariate analyses).

The authors also suggest that smoking cessation programs be placed in hospitals caring for underprivileged and indigent populations to address socioeconomic inequities. However, we wish to highlight that the