Testing homocysteine-induced neurotransmitter deficiency, and depression of mood hypothesis in clinical practice

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Abstract

Background: high total plasma homocysteine (tHcy) levels may cause neurotransmitter deficiency, and consequently depression of mood. We have recently shown that mixed oral nutritional supplements containing B-group vitamins led to a statistically significant benefit on depressive symptoms. The aim of this report was to examine the association between elevated plasma tHcy and symptoms of depression in older patients.

Methods: two-hundred and thirty-six hospitalised acutely ill older patients, who were part of a randomised double-blind placebo-controlled trial, were assigned to receive daily mixed oral nutritional supplements containing B-group vitamins or a placebo for 6 weeks. Outcome measures included symptoms of depression measured using Geriatric Depression score and plasma tHcy levels.

Results: the mean tHcy concentration fell by 22% among patients given the supplements compared with the placebo group (mean difference 4.1 µmol/l (95% CI: 0.14–8.03), P = 0.043). tHcy concentrations was divided into four quartiles and analysed against depression scores. tHcy concentrations in the first relative to the fourth quartile of the distribution were associated with a lower depression symptoms at the end of the supplement period (Geriatric depression score r = −0.20, P = 0.042).

Conclusions: lower plasma tHcy concentrations were associated with reduced depression symptoms in older patients recovering from acute illness.

Keywords: depression, homocysteine, B vitamins, older people nutrition, nutrition supplements
Introduction
There is considerable recent interest in the relevance of folate and B12 deficiencies and raised plasma Homocysteine (tHcy) to mental health in older people [1–3]. tHcy is a sulphhydril-containing amino acid derived from the metabolic demethylation of dietary methionine, which is abundant in animal protein. Homocysteine can be remethylated to methionine through the 5-methyltetrahydrofolate pathway which requires B-group vitamins mainly folic acid and B12 but to a lesser extent B6 and B2. Methionine is involved in a number of methylation reactions in the brain including DNA, RNA, phospholipids and the synthesis of neurotransmitters such as serotonin, noradrenaline and dopamine [4]. High homocysteine concentrations as a result of diminished remethylation to methionine have direct toxic effects not only to vascular endothelial cells, but also to neuronal cells hence the association between high homocysteine and a number of psychiatric illnesses including depression [4]. So the link between B-group vitamins, homocysteine and depression of mood does seem to have a plausible biological explanation [2]. Indeed a number of studies have found an association between tHcy and increased risk of depression; however, most of these studies were epidemiological or cross-sectional observational studies and cannot therefore prove a causal relationship [5–11]. Furthermore, the possibility of depression leading to poorer diet, low B vitamins and consequently high homocysteine concentrations cannot be excluded [12].

We have recently conducted a large randomised double-blind placebo-controlled trial in which we have shown that mixed nutrient supplements containing physiological doses of B-group vitamins of hospitalised acutely ill older patients improved vitamins status and led to a statistically significant benefit on depressive symptoms [13, 14]. The aim of this short report was to examine the association between elevated plasma tHcy and symptoms of depression in older patients recovering from acute illness.

Methods
Details of this randomised double-blind placebo-controlled trial have been published elsewhere [13, 14]. Briefly, patients were eligible for the study if they met the following criteria: age ≥65 years; stable medical condition; able to swallow and able to sign an informed written consent form. Patients excluded from the study were those with severe medical or psychiatric illness, dementia, malignancy, living in institution and patients already on supplements. The study was approved by local research ethics committee and informed written consent was obtained from each patient.

Treatment and placebo
The supplement group received two bottles of 200 ml each of a nutritional supplement drink daily for 6 weeks. The composition of the supplement was such as to provide, in total, 995 kcal of energy (45% carbohydrate, 35% fat, 20% protein), 1.3 mg of vitamin B2, 1.4 mg of vitamin B6, 1.5 μg of B12, 200 μg of folic acid and 100% of the reference nutrient intakes for a healthy older person for vitamins and minerals. The placebo was identical to the supplement but contained no protein or micronutrients, only a minimum calorie content of 60 kcal to make it palatable. Administration of treatment and assessment was done blind to treatment assignment, and the investigator and patients were also blinded to the ongoing results of the study. We used validated food diaries to measure dietary intakes.

Measurements
Depression
Depressive symptoms were assessed using the 15-item Geriatric Depression questionnaire (GDS). The 15-item GDS is suitable as a screening test for depressive symptoms in the elderly; ideal for evaluating the clinical severity of depression, and therefore for monitoring treatment. It is easy to administer, needs no prior psychiatric knowledge and has been well validated in many environments [15]. The GDS maximum score is 15. In clinical practice, a score of 0–4 = no depression; 5–10 = mild depression; ≥11 = severe depression.

Other measurements
Details of the sample size calculation and randomisation methods, clinical and nutritional status assessments and blood sampling and analysis have been published previously [13, 14].

Statistical analysis
Statistical analyses were performed with SPSS software, version 19.0 (SPSS, Inc., Chicago, IL, USA). Descriptive statistics including mean (SD), median, minimum and maximum values were calculated. Correlation between variables was evaluated by Pearson and Spearman correlation coefficients. Statistical comparisons between groups were carried out using independent Samples t-test. A multiple regression analysis was performed to determine the influence of tHcy on depression score at the end of the supplement period after adjusting for, treatment effect. P-value of <0.05 was considered significant.

Results
A sub-sample of 236 patients who were part of a randomised double-blind placebo-controlled trial had their plasma tHcy concentration assessed at baseline. The number of patients with repeat measurements at 6 weeks was 119. Exclusions were due to early deaths or refusal to have a repeat blood sample taken. Although there were no significant differences between responders and non-responders,
the non-responders were significantly more likely to be female ($P = 0.016$) and older ($P = 0.011$).

The mean plasma tHcy concentration was lowered by 22% among patients given the supplement drink compared with the placebo group [mean difference 4.1 µmol/l (95% CI: 0.14–8.03), $P = 0.043$] (Table 1). tHcy concentrations was divided into four quartiles and analysed against depression scores. tHcy concentrations in the first relative to the fourth quartile of the distribution were associated with a lower depression symptoms at the end of the supplement period (Geriatric depression score $r = −0.20$, $P = 0.042$) (Figure 1). Adjustment for the treatment effect using multiple regression analysis significantly reduced the association between tHcy and depression scores at the end of the supplement period ($P = 0.051$).

### Discussion

Physiological doses of B-group vitamin supplements improved vitamins status and led to a significant reduction in plasma tHcy concentration compared with the placebo group. Lower plasma tHcy concentrations were associated with lower symptoms of depression.

Many epidemiological and case–control studies have shown association between folate and vitamin B12 deficiency and depression and both folate and vitamin B12, and to a lesser extent vitamins B2 and B6 are major determinants of homocysteine metabolism and plasma tHcy concentration [2, 16, 17]. Although many of these studies including some systematic reviews have adjusted for possible confounders in the relationship between B vitamins, tHcy, and depression a causal relationship cannot be inferred because of the lack of sufficiently powered randomised controlled trials among them. In addition many of these studies have used different cohorts of subjects and/or screening tools to define depression [2, 5–11]. Another important issue is reverse causality—that is depression leading to poor appetite, smoking, excessive alcohol consumption resulting in low B-group vitamin levels and consequently high homocysteine concentrations [12]. Although current available data do not support the latter hypothesis, this question can only be answered through powerful prospective intervention trials. A recent cross-sectional study combined with a meta-analysis on the relationship between tHcy and depression has reported that higher concentrations of tHcy increase the risk of depression and that lowering tHcy could reduce the odds of depression [2].

Although nutritional deficiencies in older persons even among those who are apparently healthy are common and the impact on their physical and mental well-being is likely to be high research on the relationship between nutritional factors and psychological health is generally lacking [1]. The inclusion criteria and baseline characteristics suggest that our study population represents a better-nourished group of patients. In contrast, those who were excluded because of severe illness, dementia, supplement intake or living in institutional care were more likely to be undernourished and might therefore benefit most from nutritional support. In addition, we have only used physiological amounts of mixed nutrient supplements. This would remove any concern regarding possible harmful effects of using pharmacological doses of B vitamins. Furthermore our study sample comes from a population where low biochemical status of one or more micronutrients was reported in 40% of the population [18].

One potential limitation of this study is that findings are based on small subgroup analysis of a relatively large randomised placebo-controlled study. Although nutritional supplements led to a significant benefit on depression symptoms and reduced tHcy concentrations at the end of the supplement period, adjusting for treatment effect using multiple regression analysis significantly reduced the association between tHcy and depression scores.

In conclusion, we found a high proportion of acutely ill older patients have elevated plasma tHcy which is responsive to physiological doses of a multinutrient supplements containing B-group vitamins. Additionally, lower plasma tHcy concentrations were associated with reduced depression symptoms. Wider implementation of this strategy could have a substantial beneficial impact on older people’s health particularly those recovering from acute illness.

### Table 1. Effect of supplements on homocysteine (tHcy) levels compared with Placebo

<table>
<thead>
<tr>
<th>tHcy (µmol/l)</th>
<th>Group</th>
<th>n</th>
<th>Mean</th>
<th>SEM</th>
<th>Mean difference (95% CI)</th>
<th>P-value (two-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Placebo</td>
<td>123</td>
<td>15.2</td>
<td>0.79</td>
<td>$-3.11$</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>Supplements</td>
<td>113</td>
<td>18.3</td>
<td>1.41</td>
<td>$-6.31$–$-0.98$</td>
<td>0.056</td>
</tr>
<tr>
<td>6 weeks</td>
<td>Placebo</td>
<td>58</td>
<td>14.6</td>
<td>0.76</td>
<td>$1.33$</td>
<td>0.011</td>
</tr>
<tr>
<td></td>
<td>Supplements</td>
<td>61</td>
<td>13.2</td>
<td>0.75</td>
<td>$-0.78$–$-3.44$</td>
<td>0.215</td>
</tr>
<tr>
<td>Change in tHcy</td>
<td>Placebo</td>
<td>$-0.004$</td>
<td>0.70</td>
<td>4.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Supplements</td>
<td>$-4.08$</td>
<td>1.83</td>
<td>0.043</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 1.** Association of homocysteine levels with depression scores at the end of the supplement period.
Key points

- B-group vitamin deficiencies and raised plasma Homocysteine (tHcy) are associated with increased symptoms of depression.
- High tHcy levels may cause neurotransmitter deficiency, and consequently depression of mood.
- Mixed nutrient supplements containing physiological amount of B vitamins significantly reduced plasma tHcy concentrations in older patients.
- Lower plasma tHcy concentrations were associated with reduced depression symptoms.

Conflicts of interest

None declared.

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References


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