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## High vitamin B<sub>12</sub> level and good treatment outcome may be associated in major depressive disorder

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### Abstract

**Background:** Despite of an increasing body of research the associations between vitamin B<sub>12</sub> and folate levels and the treatment outcome in depressive disorders are still unsolved. We therefore conducted this naturalistic prospective follow-up study. Our aim was to determine whether there were any associations between the vitamin B<sub>12</sub> and folate level and the six-month treatment outcome in patients with major depressive disorder. Because vitamin B<sub>12</sub> and folate deficiency may result in changes in haematological indices, including mean corpuscular volume, red blood cell count and hematocrit, we also examined whether these indices were associated with the treatment outcome.

**Methods:** Haematological indices, erythrocyte folate and serum vitamin B<sub>12</sub> levels were determined in 115 outpatients with DSM-III-R major depressive disorder at baseline and serum vitamin B<sub>12</sub> level again on six-month follow-up. The 17-item Hamilton Depression Rating Scale was also compiled, respectively. In the statistical analysis we used chi-squared test, Pearson's correlation coefficient, the Student's t-test, analysis of variance (ANOVA), and univariate and multivariate linear regression analysis.

**Results:** Higher vitamin B<sub>12</sub> levels significantly associated with a better outcome. The association between the folate level and treatment outcome was weak and probably not independent. No relationship was found between haematological indices and the six-month outcome.

**Conclusion:** The vitamin B<sub>12</sub> level and the probability of recovery from major depression may be positively associated. Nevertheless, further studies are suggested to confirm this finding.

### Background

Low levels of vitamin B<sub>12</sub> and folate have been found in the serum and red blood cells of patients with depressive disorders [1-4]. Older, physically disabled women with metabolically significant vitamin B<sub>12</sub> deficiency have been found to have a two-fold higher risk of depression than women with normal plasma levels of vitamin B<sub>12</sub> [5]. The

findings from three recent large population-based studies are, however, contradictory [6-8].

A Dutch study (n = 3884) suggested that B<sub>12</sub> deficiency but not folate deficiency is independently related to depressive disorders [6]. Morris et al. [7] found a low folate status in depressed subjects in a sample of the general US population (n = 2948). Finally, a Norwegian study (n =

5948) suggested that neither low plasma folate nor vitamin B<sub>12</sub> levels are significantly related to depression without comorbid anxiety disorder in the general population [8].

A low folate level has been linked to a poor response to antidepressive drug therapy [4,9,10], and daily folic acid or methylfolate augmentation of antidepressive drug treatment has been reported to improve clinical and social recovery [11-14]. Thus far, no associations have been found between a low vitamin B<sub>12</sub> level and a poor treatment response in patients with depressive disorders. Nevertheless, the augmentation of antidepressive treatment with vitamins B<sub>1</sub>, B<sub>2</sub>, and B<sub>6</sub> increased vitamin B<sub>12</sub> levels in elderly patients with major depression without specific supplementation, and there were trends towards greater improvements in scores for depression ratings [15].

The clinical relevance of these findings concerning the associations between vitamin B<sub>12</sub> and folate levels and the treatment outcome in depressive disorders is still unsolved. We therefore conducted this naturalistic prospective follow-up study. Our aim was to determine whether there were any associations between the vitamin B<sub>12</sub> and folate level and the six-month treatment outcome in patients with major depressive disorder in Finland. Because vitamin B<sub>12</sub> and folate deficiency may result in changes in haematological indices, including mean corpuscular volume, red blood cell count and hematocrit, we also examined whether these indices were associated with the treatment outcome. On the basis of previous studies we hypothesized that both high vitamin B<sub>12</sub> and folate levels might be positively associated with a better treatment outcome in patients with major depressive disorder.

## Methods

The subjects were 115 outpatients with DSM-III-R major depressive disorder consecutively consulted in the Department of Psychiatry, Kuopio University Hospital, Finland. Approval for the study was obtained from the Ethics Committee of Kuopio University Hospital and the University of Kuopio. All patients provided written informed consent before entering the study.

At entry, the diagnosis of a current episode of major depressive disorder was confirmed by means of the Structured Clinical Interview for DSM-III-R, conducted by a trained interviewer [16]. Patients completed questionnaires relating to their sociodemographic background, current smoking habits (yes/no), patterns of alcohol use (used at least once a week/other), family history of depression (one or both parents have been treated for depression; yes/no) and the duration of depressive illness (years from the first episode of depressive symptoms). Patients'

weights and heights were also measured, and body mass index (BMI) was calculated.

There were 70 females (61%) and 45 males (39%) in the sample, with a mean age of 43.9 (SD 10.9, range 21 – 69) years. Thirty-one of the patients (27%) had a positive family history of depressive disorders. The first episode of depressive symptoms had occurred on average 9.6 (SD 10.2) years before. Twenty-four per cent of the patients were current smokers (n = 27) and twenty-six per cent used alcohol weekly (n = 30). None of these variables associated with the treatment outcome (see classification later).

At entry, the serum vitamin B<sub>12</sub> and erythrocyte folate level as well as haemoglobin (Hb), mean corpuscular volume (MCV), red blood cell count (RBC) and hematocrit (HCR) were determined in each patient. After preliminary baseline analyses, it was decided to determine serum B<sub>12</sub> from serum samples that had been stored at -20°C on the six-month follow-up.

Serum vitamin B<sub>12</sub> and erythrocyte folate levels were determined using time-resolved fluoroimmunoassays in the laboratory of Kuopio University Hospital. Reference ranges, which were provided by the laboratory, were 140 – 540 pmol/l for a normal serum vitamin B<sub>12</sub> level and 315 – 850 nmol/l for a normal erythrocyte folate level. Levels below these ranges were defined as low, and above these ranges as high.

The level of depression was assessed using the 17-item Hamilton Depression Rating Scale (HDRS) both at baseline and after six months [17]. Cronbach's alpha for HDRS ratings was 0.74 at baseline and 0.81 on follow-up. The mean HDRS score at baseline was 18.8 (SD 6.5), and the mean decline in the HDRS score during the study period was 6.8 (SD 7.4). The treatment outcome was defined in the following manner: a full response was defined as a reduction of more than 50% in the HDRS score between baseline and follow-up, a partial response as a reduction of between 25 and 50%, and nonresponse as a reduction of less than 25% [18]. Symptoms of weight loss and gastrointestinal symptoms, including poor appetite, were derived from HDRS ratings for statistical analyses.

For this study the patients were interviewed at baseline and on 6-month follow-up. During the study period they were treated by their regular outpatient psychiatrists and therapists. Information on the treatment received during the study period was collected from patients' case notes and follow-up interviews. The antidepressive medication used during the study period was considered to be adequate if the length of the treatment exceeded 3 months

**Table 1: Haematological indices, vitamin B<sub>12</sub> and folate, and six-month treatment outcome in major depressive disorder (n = 115)**

	Nonresponse (n = 40)	Partial response (n = 34)	Full response (n = 41)
	Mean (SD)	Mean (SD)	Mean (SD)
Haemoglobin (g/l)	141.7 (10.1)	141.1 (13.3)	139.1 (14.8)
Mean corpuscular volume (fl)	92.5 (6.0)	90.4 (5.8)	89.5 (6.6)
Red blood cell count (cell <sup>12</sup> /l)	4.51 (0.46)	4.57 (0.39)	4.56 (0.42)
Hematocrit (%)	41.6 (3.1)	41.2 (3.7)	40.8 (4.0)
Vitamin B <sub>12</sub> at baseline (pmol/l) <sup>1</sup>	347.2 (103.4)	396.0 (108.4)	439.1 (115.6)
Vitamin B <sub>12</sub> on follow-up (pmol/l) <sup>2</sup>	280.4 (93.3)	316.2 (98.2)	338.8 (87.5)
Folate at baseline (nmol/l)	409.7 (126.0)	431.5 (114.8)	446.8 (244.8)
HDRS score at baseline <sup>3</sup>	16.8 (7.2)	22.3 (5.6)	17.8 (5.4)
HDRS score on follow-up <sup>4</sup>	17.6 (4.9)	13.8 (3.7)	4.6 (3.2)

ANOVA: <sup>1</sup>F = 7.17, p = 0.001. <sup>2</sup>F = 4.07, p = 0.02. <sup>3</sup>F = 8.10, p = 0.01. <sup>4</sup>F = 112.58, p < 0.001.

and if the daily dose used was within the range deemed efficient (tricyclics  $\geq$  150 mg, citalopram  $\geq$  20 mg, fluoxetine  $\geq$  20 mg and paroxetine  $\geq$  20 mg) [19,20]. Patients were asked whether they had had an adjunct therapeutic relationship during the study period. The frequency and length of the therapeutic relationship and the presence of inpatient care received during the follow-up were also recorded.

Comparisons were made between patients in full response (n = 40), partial response (n = 34) and nonresponse (n = 41) groups. The statistical methods used were chi-squared test, Pearson's correlation coefficient, the Student's t-test, analysis of variance (ANOVA), and univariate and multivariate linear regression analysis.

## Results

At baseline, no patients had a low vitamin B<sub>12</sub> level, while 14 patients (12%) had a high vitamin B<sub>12</sub> level. Twenty-one patients (18%) had a low erythrocyte folate level and two (2%) had a high level. On follow-up, two patients (2%) had a low and two (2%) a high vitamin B<sub>12</sub> level. Baseline and 6-month B<sub>12</sub> levels correlated significantly (r = 0.52, p < 0.001).

Haematological indices and the BMI did not correlate with vitamin B<sub>12</sub> or folate levels. Neither were there significant differences in the levels of vitamin B<sub>12</sub> or folate between patients with and without weight loss or gastrointestinal symptoms (data not shown). Furthermore, haematological indices did not associate with the treatment response (Table 1).

Significant differences were found in B<sub>12</sub> levels between patients in full response, partial response and nonresponse groups (Table 1). The vitamin B<sub>12</sub> level and the HDRS score did not correlate at baseline. Nevertheless, a

positive correlation was found between both the vitamin B<sub>12</sub> level at baseline (r = 0.39, p < 0.001) and on follow-up (r = 0.26, p = 0.006), and the decline in the HDRS score during six months of treatment.

There were no significant differences in the erythrocyte folate level at baseline between full response, partial response and nonresponse groups (Table 1). Nevertheless, the folate level at baseline correlated with both the baseline HDRS score (r = 0.21, p = 0.021) and the decline in the HDRS score during the follow-up (r = 0.20, p = 0.037).

The severity of depression (HDRS score) at baseline differed between full response, partial response and nonresponse groups. The highest score was in the partial response group. Not surprisingly, a highly significant difference was also found between the groups in the follow-up HDRS score (Table 1).

Sixty-four patients (56%) had been on adequate antidepressive medication and 83 (72%) had had an adjunct therapeutic relationship. However, only 49 of them (43% of the total sample) had been met at least weekly during three months. Fifteen (13%) had been treated as inpatients during the follow-up period. These treatment variables did not associate with haematological indices, the erythrocyte folate level, the serum vitamin B<sub>12</sub> level or the baseline HDRS score (data not shown). Those who were in nonresponse and partial response groups had been treated as inpatients more often than those in the full response group. No other associations were found between treatment variables and response groups (Table 2).

**Table 2: Treatment variables and six-month outcome in major depressive disorder (n = 115)**

	Nonresponse (n = 40)	Partial response (n = 34)	Full response (n = 41)
	N (%)	N (%)	N (%)
Adjunct therapeutic relationship	30 (73)	24 (71)	29 (73)
Weekly psychotherapy <sup>1</sup>	20 (49)	11 (32)	18 (45)
Adequate drug therapy <sup>2</sup>	26 (63)	20 (59)	18 (45)
Treated as an inpatient <sup>3</sup>	9 (22)	5 (15)	1 (3)

<sup>1</sup> Duration at least three months. <sup>2</sup> See definition in the Methods section. <sup>3</sup> Chi-Squared 6.87, df 2, p = 0.032.

Haematological indices did not associate with the decline in the HDRS score according to linear regression analysis (data not shown).

The relationship between the baseline vitamin B<sub>12</sub> level and the decline in the HDRS score was found to be positive and linear in univariate regression analysis ( $\beta = 0.39$ ,  $t = 4.50$ ,  $p < 0.001$ ). This relationship remained independent and significant ( $\beta = 0.28$ ,  $t = 3.40$ ,  $p = 0.001$ ) even after adjustment for age (years), sex, duration of the illness (years), family history of depression (yes/no), patterns of alcohol use (at least once a week/other), smoking habits (daily/other), BMI (kg/m<sup>2</sup>), weight loss (less than 3 kg, 3–5 kg, 5–8 kg, over 8 kg), gastrointestinal symptoms (yes/no), severity of depression at baseline (HDRS score), adequate drug treatment (yes/no), weekly psychotherapy (yes/no) and inpatient treatment (yes/no). For the follow-up vitamin B<sub>12</sub> level the figures were also statistically significant (univariate  $\beta = 0.26$ ,  $t = 2.80$ ,  $p = 0.006$  and multivariate  $\beta = 0.24$ ,  $t = 2.85$ ,  $p = 0.006$ , respectively).

The baseline folate level and decline in the HDRS score associated weakly in univariate linear regression analysis ( $\beta = 0.20$ ,  $t = 2.11$ ,  $p = 0.037$ ), but the association was no more significant when adjusted for other variables included in the multivariate analyses ( $\beta = 0.08$ ,  $t = 0.87$ ,  $p = 0.389$ ).

**Discussion**

As far as we know, there have been no previous studies that have suggested a positive relationship between the vitamin B<sub>12</sub> level and the treatment outcome in patients with major depressive disorder who generally have normal or high serum vitamin B<sub>12</sub> levels. Previous research has focused on possible associations between a low vitamin B<sub>12</sub> level and a poor treatment response [9]. A low vitamin B<sub>12</sub> level was less common in our sample than has been previously reported in patients with major depression [21]. We found no correlation between the severity of depression and the level of vitamin B<sub>12</sub> at baseline, although the folate level and severity of depression dis-

played a weak positive correlation. Engström et al. [22] found no correlation between the levels of folate or B<sub>12</sub> and the severity of depression, but an inverse relationship between the level of folate and severity of depression has been reported in some other studies [3,9].

A low folate level was relatively common (18%) among our patients with major depressive disorder, which is in accordance with previous studies [23]. Nevertheless, a low folate level was not detected in German or Chinese patients with major depression [24,25]. We observed only weak indications that a low erythrocyte folate level might be associated with the poor treatment outcome, which is contradictory to some previous studies [4,9,10]. It could be that culturally defined dietary habits influence the relationship between the folate status and depression in different societies [25]. Recently it was reported that low dietary folate and depressive symptoms are associated in middle-aged Finnish men [26]. Moreover, our study included only young and middle-aged outpatients with moderate depression, which may have influenced the results. The association between folate and depression may be more prominent in elderly subjects, among whom folate deficiency has been relatively common in some studies [27].

Poor appetite and inappropriate food intake as symptoms of depression could result in low levels of vitamin B<sub>12</sub> and especially low levels of folate. However, we found no connection between BMI, HDRS items relating to gastrointestinal symptoms and weight loss, and blood vitamin levels. Why some depressed people have lower levels of these vitamins could be a topic for further investigation. It might reflect to a lower intake of vitamins from food or assimilation from the gastrointestinal track, or a higher rate of metabolism of these vitamins. Depression may also affect the quality of food in the diet. Morris and co-workers [7] found that levels of blood folate had decreased after an episode of depression. However, loss of appetite, weight loss and being underweight were not related to folate levels.

There are several theories concerning potential associations between depression and levels of vitamin B<sub>12</sub> and folate. Vitamin B<sub>12</sub> and folate are connected with the synthesis of monoamines and are involved in single carbon transfer methylation reactions connected with the production of monoamine neurotransmitters [28]. Low levels of 5-hydroxyindole acetic acid (5-HIAA) in cerebrospinal fluid (CSF) have been found in depressed patients with folate deficiency [29]. However, Engström et al. [22] found no correlation between levels of 5-HIAA in the CSF and vitamin B<sub>12</sub> or folate levels.

Vitamin B<sub>12</sub> deficiency may also result in the accumulation of homocysteine, which has been suggested to lead to exito-toxic reactions and may enhance depression [30,31]. Bottiglieri et al. [32] found raised levels of homocysteine in 52% of depressed inpatients. Vitamin B<sub>12</sub> is also required in the synthesis of S-adenosylmethionine (SAM), which is needed as a methyl donor in many methylation reactions in the brain. It has been also suggested to have antidepressant properties [33].

We observed no correlation between vitamin B<sub>12</sub> and folate levels and the mean corpuscular volume, red blood cell count or hematocrit, which is in line with previous studies [5,21]. Haematological indices did not predict the treatment outcome, either. This indicates that haematological indices have no value in assessing depressed patients, while the levels of vitamin B<sub>12</sub> in serum and folate in erythrocytes may have.

Multivariate analyses adjusted for age, sex, the family history of depression, the duration of the illness, severity of depression at baseline and treatment variables during the follow-up period supported the existence of an independent relationship between the vitamin B<sub>12</sub> level and decline in the HDRS score. This was, however, a naturalistic follow-up study, and sociodemographic and clinical and treatment variables were not controlled a priori. This is the main shortcoming of our study. We suggest further studies with controlled illness and treatment variables to confirm or to refute our findings.

Our sample included more women (61%) than men, only one subject was aged over 65 years and 87% had only been treated as outpatients. All these variables may influence the results. Men and women may have different dietary habits. A low folate intake is common among Finnish men [26]. A low vitamin B<sub>12</sub> level and B<sub>12</sub> deficiency have been found to be common among older women [5], but elderly men may have even lower B<sub>12</sub> levels [34]. Finally, patients with psychotic depression may have lower B<sub>12</sub> levels than non-psychotic depressives [35]. Psychotic depression is a common indication for inpatient treatment. For all these reasons one should be careful about

generalizing these findings to all groups of depressive patients.

The mean level of vitamin B<sub>12</sub> on follow-up was lower than at baseline, which may indicate some deterioration of the samples during freezing. Previously, Kirke et al. have reported that levels of folate may decline by approximately 20% during six years of freezing [36]. The length of the storage had little effect on this deterioration. Another explanation is that depression may also affect the quality of food in the diet which lowers levels of blood vitamins during an episode of depression [7]. Nevertheless, baseline and follow-up levels of vitamin B<sub>12</sub> in the present study correlated significantly and both also associated highly significantly with the decline in the HDRS level during the follow-up, which supports our findings.

## Conclusions

The results of this and previous studies together suggest that the associations between folate, vitamin B<sub>12</sub> and depression remain unresolved. It is possible that there are several biological pathways leading to major depressive disorder, which is still defined as a cluster of unspecific clinical symptoms. Further epidemiological and clinical studies on the associations between folate, vitamin B<sub>12</sub> and depressive disorders are suggested. It is possible that safe augmentation strategies for antidepressive treatments could be found.

## Competing interests

None declared.

## Authors' contribution

JH performed the statistical analysis and drafted the manuscript. TT and AT participated in the study design and reviewed all versions of the manuscript. HV conceived the study project and participated in its design and coordination. All authors read and approved the final manuscript.

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