

The comparison of folate and vitamin B12 levels between depressive and nondepressive postmenopausal women

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Background/aim: To investigate if there is any association between the serum folate and vitamin B12 status and the depressive symptoms in postmenopausal women.

Materials and methods: The study included 95 postmenopausal women. The Center for Epidemiologic Studies Depression Scale (CES-D) was used to assess their depressive symptoms. The investigated women were classified into 2 groups based on the existence of depressive symptoms. These 2 groups were compared in terms of folic acid and vitamin B12 levels.

Results: Among 95 cases, 27 postmenopausal women scored 16 or more on the CES-D scale and were classified as the depressive group (Group 1), and 68 postmenopausal women scored 15 or less and were classified as the nondepressive group (Group 2). The serum levels of folate were 11.5 ± 5.4 ng/mL in group 1 and 12.3 ± 5.3 ng/mL in group 2. The concentrations of vitamin B12 were 456.2 ± 343.4 pg/mL in group 1 and 446.5 ± 165.1 pg/mL in group 2. The folate and vitamin B12 levels did not significantly correlate to the frequency of depressive symptoms ($P = 0.52$ and $P = 0.24$, respectively).

Conclusion: In this study, no correlation was detected between serum folate and vitamin B12 levels and depressive symptoms in postmenopausal women. Supplementation of folic acid and vitamin B12 for postmenopausal women does not seem to be an effective intervention to reduce depressive symptoms.

Key words: Depressive symptoms, folate, menopause, vitamin B12

1. Introduction

Menopause is a physiologic period during which estrogen production in the ovaries ends and many climacteric symptoms, including depression, may arise (1). Depression may be debilitating, and many patients may not respond to antidepressant treatment or may discontinue drug therapy due to side effects. An improved response to antidepressants is reported in women when administered in combination with folic acid supplements; thus, folate status might be related to depression (2). It has been reported that disturbances in folate-dependent one-carbon metabolism may contribute to neurodegenerative diseases, including depression (3). Slapien et al. suggested that folate and possible methionine metabolism involvement may play a significant role in the development of depression in postmenopausal women (4). Folate, a naturally occurring B vitamin, is necessary for the synthesis of the trimonoamine

neurotransmitters implicated in depression and may enhance the effects of a traditional antidepressant (5). The active metabolite of folate is required for the remethylation of homocysteine in the production of methionine, which is involved in a number of biochemical processes involving the monoamine neurotransmitters serotonin, norepinephrine, and dopamine (6). Thus, a deficiency in folate may disturb the production and function of these neurotransmitters. A deficiency of either folate or vitamin B12 causes elevated homocysteine concentrations, which may contribute to the pathogenesis of a major depressive disorder (7). The Rotterdam study of older men and women found that hyperhomocysteinemia, vitamin B12 deficiency, and folate deficiency were related to depressive disorders (8). Nanri also suggested an inverse relationship between serum folate and 25-hydroxyvitamin D levels and depressive symptoms (9).

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In light of these findings, supplementation of vitamins may offer hope as a safe and effective intervention to reduce the burden of depression. Since depression is frequently observed in the postmenopausal period and significantly deteriorates life quality, it is important to overcome depression during this period. There are studies in the literature evaluating the relationships among folate, vitamin B12, and depressive symptoms; in this study, we especially aim to clarify the association between the serum folate and vitamin B12 status and the depressive symptoms in the postmenopausal period and to make a consideration about supplementation of folic acid and vitamin B12.

2. Materials and methods

The study included 95 postmenopausal women. It was carried out in the Yenimahalle State Hospital between August 2010 and February 2011. All women were at least 1 year postmenopausal. Patients on a fortified diet containing folate or vitamin B12 and taking folate or vitamin B12 supplements; with malabsorption disorders; who had a history of psychological care or treatment; or who were receiving hormone replacement therapy were excluded from the study. Informed consent was received from all patients enrolled in the study. The Turkish version of the Center for Epidemiologic Studies Depression Scale (CES-D) (10) was used to assess the women's depressive symptoms (Table 1). It is a self-report scale used to measure the severity of depressive symptoms. Participants scored the frequency of depressive symptoms in the week prior to assessment. Total CES-D scores range from 0 to 60. A total score of 16 or higher was considered depression. Serum folate and vitamin B12 concentrations were measured in all cases. Vitamin B12 (reference range: 211–911 pg/mL) and folate (reference range: 5.38–24 ng/mL) levels were measured by autoanalyzer. The investigated women were classified in 2 groups based on the existence of depressive symptoms according to the CES-D scale. These 2 groups were compared in terms of folic acid and vitamin B12 status.

The normal distribution of the quantitative data was evaluated by the Shapiro–Wilks test. In normally distributed data, the variability between the 2 groups was evaluated by independent samples t-test. In the data that were not normally distributed, the variability of the 2 groups was evaluated by the Mann–Whitney U test. Numerical data were presented as mean \pm standard deviation. A P-value of ≤ 0.05 was accepted as statistically significant. Data analysis was performed using SPSS 16.0.

3. Results

Among 95 cases, 27 postmenopausal women scored 16 or higher on the CES-D scale and were considered as the depressive group (Group 1). The remaining 68

postmenopausal women scored 15 or lower and were considered as the nondepressive group (Group 2).

The average age of patients (range: 41–73 years) was 50.5 ± 5.3 years in group 1 and 52.3 ± 7.0 years in group 2 ($P = 0.23$). There were no statistically significant differences between the 2 groups in terms of age, smoking, and duration of menopause (Table 2).

There were 3 surgical and 24 natural menopause cases in group 1 and 9 surgical and 59 natural menopause cases in group 2. There was no statistically significant relationship between menopause type and depression ($P = 0.54$).

The serum levels of folate were 11.5 ± 5.4 ng/mL in group 1 and 12.3 ± 5.3 ng/mL in group 2. The concentrations of vitamin B12 were 456.2 ± 343.4 pg/mL in group 1 and 446.5 ± 165.1 pg/mL in group 2. There were no folate- or vitamin B12-deficient patients in group 1. In group 2, 1 patient had folate deficiency and 2 patients had vitamin B12 deficiency. Serum levels of folate and vitamin B12 were not significantly different between depressive and nondepressive postmenopausal women ($P = 0.52$ and $P = 0.24$, respectively).

There were 9 smokers (who smoke every day, independent of the number of cigarettes per day) and 18 nonsmokers in group 1 and 13 smokers and 55 nonsmokers in group 2. There was no statistically significant relationship between smoking and depression ($P = 0.11$).

There was also no statistically significant relationship between duration of menopause period and levels of folate and vitamin B12 ($P = 0.20$ and $P = 0.24$, respectively). However, a statistically significant relationship was found between folate and vitamin B12 levels ($P = 0.017$).

4. Discussion

The transition to menopause and its changing hormonal milieu are associated with an increased risk of depressed mood, not only for those with a history of depression but also for women with no history of depression, supporting the hypothesis that menopausal transition is a period of vulnerability framed by the changing hormonal status of ovarian aging (11). Bromberger et al. suggested that the risk for depressive symptoms increased with the menopausal transition, stayed elevated through early postmenopause, and was independent of relevant demographic, psychosocial, behavioral, and health factors (12). Conversely, there was no significant relationship between duration of menopausal period and depressive symptoms in our study.

It has been suggested that folate and vitamin B12 have a role in depression, but the results of epidemiologic studies on this issue have been inconsistent. It is hypothesized that the deficiencies in folate and vitamin B12 can lead to elevated homocysteine concentrations, which have been associated with depression (13–17). The consumption of certain

Table 1. The Center for Epidemiologic Studies Depression Scale (CES-D) (10).

Center for Epidemiologic Studies Depression Scale (CES-D), NIMH

Below is a list of the ways you might have felt or behaved. Mark how often you have felt this way during the past week.

	During the Past Week			
	Rarely or none of the time (less than 1 day)	Some or a little of the time (1–2 days)	Occasionally or a moderate amount of time (3–4 days)	Most or all of the time (5–7 days)
1. I was bothered by things that usually don't bother me.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. I did not feel like eating; my appetite was poor.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. I felt that I could not shake off the blues even with help from my family or friends.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. I felt I was just as good as other people.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. I had trouble keeping my mind on what I was doing.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. I felt depressed.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. I felt that everything I did was an effort.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. I felt hopeful about the future.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. I thought my life had been a failure.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. I felt fearful.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11. My sleep was restless.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12. I was happy.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13. I talked less than usual.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14. I felt lonely.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
15. People were unfriendly.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16. I enjoyed life.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
17. I had crying spells.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
18. I felt sad.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
19. I felt that people dislike me.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
20. I could not get "going."	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

SCORING: Zero for answers in the first column, 1 for answers in the second column, 2 for answers in the third column, 3 for answers in the fourth column. The scoring of positive items is reversed. Possible range of scores is 0 to 60, with higher scores indicating the presence of more symptomatology.

Table 2. The characteristics and findings of patients included in the study.

	Group 1	Group 2	P-value
Age (years)	50.5 ± 5.3	52.3 ± 7.0	0.23
Duration of menopause period (years)	3.6 ± 3.7	5.1 ± 6.0	0.36
Smokers/nonsmokers	9/18 (33.3%)	13/55 (19.1%)	0.11
Folate (ng/mL)	11.5 ± 5.4	2.3 ± 5.3	0.52
Vitamin B12 (pg/mL)	465.2 ± 343.4	446.5 ± 165.1	0.24

The variability between the 2 groups was evaluated by independent samples t-test.

vitamin B complexes, through diet or supplementation, decreases the total plasma concentration of homocysteine and may enhance responses to standard antidepressant treatment. Treatment with vitamin B complexes can reduce the long-term prevalence of depression in at-risk people, such as stroke survivors (18). Brocardo et al. suggested that folate has a synergistic antidepressant-like effect with fluoxetine, probably via serotonergic and noradrenergic systems (19). Folic acid is a promising nutrient in the augmentation of depression treatment efficiency, but there are not enough data for prescription of folic acid as an aid in patients with depression. Lazarou et al. suggested that folic acid levels should be examined in individuals at increased risk for folic acid deficiency, as well as in patients who do not respond to pharmaceutical treatment (20).

On the other hand, Nanri et al. suggested that while higher serum folate was associated with decreased prevalence of depressive symptoms in men, such a relationship was not observed in women (21). Walker et al. reported that neither folic acid plus vitamin B12 nor physical activity were effective in reducing depressive symptoms (22). Watanabe et al. found no significant associations between the incidence of depression and serum folate and homocysteine levels in the first trimester of pregnancy and reported that folate and homocysteine concentrations and folate consumption may not be protective against depression in early pregnancy (23). Miyake et al. (24) reported that no significant association was observed between the intake of folate and the risk of postpartum depression. In addition, Penninx et al. found no association between folate or homocysteine and depression (25).

Likewise, we also found no statistically significant relationship between depressive symptoms and either folate or vitamin B12 level in postmenopausal women in our study. Depressive symptoms in the postmenopausal women may have been affected by the presence of chronic

diseases, cognitive impairment, and flushing that drives the beginning or worsening of preexisting mood symptoms, making it difficult to find an association with serum folate and vitamin B12 levels. It was suggested that hot flushes and poor sleep independently predicted major depressive disorders (26). On the other hand, Leung and Kaplan suggested that several nutrient deficiencies, including folate deficiency, may be both a cause and a result of mood problems (2). However, study of the effects of a specific nutrient deficiency is usually affected by multiple deficiencies in an undernourished subject. This may be a cause of residual discrepancy in the studies that focus only on folate or vitamin B12 status. This may also be the cause of the relationship between folate and vitamin B12 levels found in our study.

The major limitation of our study was that we were not able to examine the risk factors for depression, such as social factors (27), history of depression, lack of partner, or family violence (28,29). The CES-D scale evaluates frequency of depressive symptoms only in the previous week; lack of evaluation and diagnosis by a psychiatrist is also another limitation. Nonidentified medications like methotrexate, trimethoprim, or anticonvulsants (30) and factors interfering with folate and vitamin B12 levels (31) may also affect the results.

The studies on this issue have conflicting results, probably because of the multiple factors affecting depression, nutrient intake, and multiple nutrient deficiencies simultaneously seen in undernourished subjects. In addition, postmenopausal symptoms may also affect our results. In conclusion, in this study, no correlation was detected between serum folate or vitamin B12 levels and depressive symptoms in postmenopausal women, and the supplementation of folic acid and vitamin B12 for postmenopausal women does not seem to be an effective intervention to reduce depressive symptoms.

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