ORIGINAL ARTICLE

Year: 2020
Volume: 7
Issue Number: 3
Doi : 10.4103/jnbs.jnbs_32_20

Received 04.11.2020
Accepted 12.11.2020
JNBS, 2020, 7(3):160-165

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VITAMIN B12 AND FOLIC ACID IN DEPRESSION AND ANXIETY: A PILOT STUDY

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Ethics committee approval: The non-interventional research ethics committee approved this study at Uskudar University (Code: 61351342-/2019-80; date: 27.02.2019).

Abstract

The association between nutrition and mental diseases has been extensively studied. Vitamin B12 and folic acid are the main vitamins in the development of the central nervous system. This study aimed to investigate the relationship between vitamin B12 and folic acid levels with depression and anxiety.

A total of 150 patients (77 with anxiety and 73 with depression) between 18 and 79 were enrolled. The initial mood state was evaluated using Beck's Depression Inventory-II (BDI-II) and Beck's Anxiety Inventory (BAI) for the presence of depression and anxiety, respectively. Venous blood samples were collected after overnight fasting and vitamin B12 and folic acid levels were measured.

Serum concentrations of folic acid were significantly lower in patients with depression than those with anxiety (p=0.04). Substantially higher vitamin B12 levels were described in men than females counterparts with severe depression (p=0.049). Additionally, there was a significant inverse correlation between folic acid levels and Beck's inventory score among patients with severe depression (r=-0.250, p=0.049).

Serum levels of vitamin B12 and folic acid could be used as markers that assess anxiety and depression's therapeutic efficiency.

Keywords: mood disorders; beck's depression inventory score, vitamin b12; folic acid, anxiety, depression

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1. Introduction

Depression and anxiety are considered the most prevalent mental diseases, resulting in the loss of the affected individuals' socioeconomic productivity. Therefore, the effective treatment of these disorders should be included as coherent chronic disease management (Chisholm et al., 2016). During the past decade, various epidemiological studies have been conducted to investigate the relationship between nutritional patterns and individuals' mental status so that dietary habits have been suggested as an underlying cause to onset the psychiatric symptoms (Owen & Corfe, 2017). In this regard, "nutritional psychology" mainly focuses on nutrition or a single nutrient on mood disorders, including depression and anxiety (Jacka, 2017). The most frequent nutritional-related deficiencies in mental diseases include ω-3 fatty acids, vitamin B family, mineral elements, and amino acids, which are the neurotransmitters precursors in the nervous system (Coppen & Bolander-Gouaille, 2005).

Vitamin B12 and folic acid as the main water-soluble vitamins play a crucial role in the central nervous system (CNS) development and health (Reynolds, 2006). Vitamin B12 and folic acid have a shared metabolism so that the deficiency in one vitamin impairs the other vitamin function (Black, 2008). There are two main mechanisms proposed for the role of vitamin B12 and folic acid in CNS development: i) The role of these vitamins in the myelination process and ii) methionine synthesis from homocysteine (h-Cys) as a crucial amino acid in neural tube formation and development (Black, 2008). Moreover, folate deficiency increases h-Cys and decrease S-adenosylmethionine (SAMet), causing methylation capacity reduction and finally alters neurotransmitter synthesis (Morris, Trivedi, & Rush, 2008).

However, the role of these vitamins in depression and anxiety management remains controversial. It has been reported that patients with low folate levels show a mean longer time for depression improvement compared to individuals with normal folate levels. Additionally, the relapse rate was also higher in patients with low folate levels (Papakostas et al., 2004). Furthermore, increases in the blood folate levels during antidepressive treatment significantly improved the Hamilton depression scale score. A higher blood folate concentration was also observed after the treatment in "responding" than that of "nonresponding" patients (Martínez-Cengotitabengoa & González-Pinto, 2017). Sepehrmanesh et al. (Sepehrmanesh, Omidi, & Gholampoor, 2017) reported that folic acid supplementation in major depressive disorder improves the antidepressant response in these patients be considered as a complementary treatment. However, Walker et al. showed no significant improvement in depressive symptoms following folic acid administration (Walker et al., 2010).

On the other hand, recent literature has also indicated the link between vitamin B12 deficiency and depression (Syed, Wasay, & Awan, 2013). High serum vitamin B12 levels have reported being associated with satisfactory treatment outcomes; however, high h-Cys levels, which is usually observed in folate/vitamin B12 deficiency in depressive patients, are typically associated with inadequate response to antidepressant therapy (Hintikka, Tolmunen, Tanskanen, & Viinamäki, 2003; Sachdev et al., 2005). Syed et al. (Syed et al., 2013) reported a significant improvement in depressive symptoms after vitamin B12 supplementation combined with antidepressants. In contrast, in a two-year vitamin B12 supplementation study, no significant improvement in depressive symptoms was observed in adult patients. However, a beneficial effect on health-related quality of life (HR-QoL) was reported in this research (De Koning et al., 2016). Vitamin B12 and folic acid supplementation also have improved the Hamilton depression and anxiety scores in human immunodeficiency virus (HIV)-positive patients (Adhikari et al., 2016).

According to a recent report, the vitamin B12, not the folic acid concentrations, were inversely correlated with the severity of depression (Skarupski et al., 2010). This study examined the association between the serum concentrations of these two nutrients and the severity of mood disorders observed in individuals of both sexes over a wide range of ages.

2. Materials and Methods

The non-interventional research ethics committee approved this study at Uskudar University (Code: 61351342-/2019-80; date: 27.02.2019).

2.1. Patients

Seventy-seven patients with anxiety and 73 patients with depression referred to the Neuropsychiatry Clinic at Uskudar University were screened and enrolled in this study from March to December 2018. The patients with overlapping characteristics of depression and anxiety were excluded. History of serum vitamin B12 and folic acid altering diseases such as hepatic dysfunction, renal disorders, diabetes mellitus, or current use of the mentioned vitamins supplements were also considered as exclusion criteria.

2.2. Clinical assessments

The psychiatric examination of the patients was done using Beck's Depression Inventory-II (BDI-II) and Beck's Anxiety Inventory (BAI) for the presence of depression and anxiety, respectively, and the scales were validated in Turkey (Mustafa, Sahin Nesrin, & Husnu, 1998; Yildirim & Ilhan, 2010). These tests contained 21 multiple choice questions with a maximum score of 3 for each item. The patients performed the tests under the supervision of a psychologist. BDI-II scores ≤9 was considered as no depression. Depression severity was also categorized as mild (BDI-II 10–15), moderate (BDI-II 16–23), and severe (BDI-II ≥24). BAI scores of <15, was also considered as unfavorable for anxiety; mild (BAI scores 16–22), moderate (BAI scores 23–42), and severe (BAI scores ≥43). Patients with BDI-II ≤9 and BAI<15 scores were excluded from the study.

2.3. Sampling and biochemical assay

Serum folic acid and vitamin B12 were measured after overnight fasting in all subjects using a Roche Cobas e411 (Mannheim, Germany) instrument. Low serum vitamin B12 (<200 pg/ml) and folic acid (<2.2 ng/ml) levels were considered as deficiency.

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2.4. Sample size determination and Statistical analysis

The sample size was determined to establish a power of 80% and a confidence interval of 95%, using the following formula: sample size=Z1-α/22*P(1-P) /d2. Data were analyzed using the statistical package for social sciences (SPSS® version 23, IBM Inc., Chicago, IL). The numerical variables were expressed as mean ± standard deviation (SD). If a normal distribution was not detected with the Kolmogorov-Smirnov test, the variables were analyzed with a non-parametric Kruskal Wallis test to compare the mean differences between groups. Additionally, bivariate correlation analysis was performed to assess the association between clinical variables and vitamin B12 or folic acid levels. P values <0.05 were considered as statistically significant.

3. Results

3.1. Demographics and general characteristics of participants:

There were 77 patients with anxiety and 73 patients diagnosed with depression. The median, range, and proportion of vitamin B12 and folic acid deficient individuals are presented in Table 1. Vitamin B12 and folic acid concentrations were significantly lower in subjects with depression than those with anxiety (p=0.04). However, there were no differences in serum concentrations of vitamin B12 and folic acid in patients with anxiety or depression when the subjects grouped according to their age (Table 2). An analysis of gender subgroups revealed that vitamin B12 and folic acid were similar between the patients of both sexes. However, men with depression had marginally higher levels of vitamin B12 than female patients with depression (p=0.049) (Table 3)

Table 1. General characteristics of individuals

Parameters		Anxiety (n=77)	Depression (n=73)
Age (year)	18-40	47	51
	41-60	26	21
	61-79	4	1
Vit B12 (pg/ml)	Median	210	267
	Range	33 -1399	112 -1451
	Deficient patients	17	25
Folic acid (ng/ml)	Median	6.1	3.9
	Range	1.5 - 16.9	1 - 15.5
	Deficient patients	5	16
Beck.Depression	Median	15	31
	Range	2 - 46	12 - 46
Beck.Anxiety	Median	28	18
	Range	10 - 43	6 - 60

Table 2. Comparison of biochemical indices between anxiety and depression groups and sub-groups

Parameters	Anxiety (n=77)	Depression (n=73)	p
Vit B12 (pg/ml)	356 ± 212	321 ± 210	0.112
Folic acid (ng/ml)	6.3 ± 3.2	5.4 ± 3.5	0.040*
Anxiety (n=77)			
	Mild anxiety (n=18)	Moderate anxiety (n=59)	P
Vit B12 (pg/ml)	314 ± 137	370 ± 229	0.890
Folic Acid (ng/ml)	6.3 ± 3.8	6.3 ± 3.0	0.584
Depression (n=73)			
	Moderate depression (n=12)	Severe depression (n=61)	P
Vit B12 (pg/ml)	381 ± 172	313 ± 216	0.081
Folic acid (ng/ml)	6.8 ± 3.1	5.2 ± 3.6	0.178

Data are presented as mean±SD. p<0.05 was considered as statistically significant.

Table 3. Comparison of biochemical indices between male and female individual through anxiety and depression sub-groups

Parameters	Anxiety sub-groups (n=77)	Male	Female	p
Vit B12 (pg/ml)	Mild anxiety (n=18)	356 ± 129	260 ± 135	0.131
	Moderate anxiety (n=59)	349 ± 233	396 ± 227	0.410
Folic acid (ng/ml)	Mild anxiety (n=18)	5.8 ± 3.0	7.0 ± 4.8	0.790
	Moderate anxiety (n=59)	6.0 ± 2.6	6.7 ± 3.5	0.521
	Depression sub-groups (n=73)	Male	Female	p
Vit B12 (pg/ml)	Moderate depression (n=12)	356 ± 192	396 ± 174	0.705
	Severe depression (n=61)	347 ± 166	297 ± 237	0.049*
Folic Acid (ng/ml)	Moderate depression (n=12)	5.4 ± 3.2	7.5 ± 2.9	0.257
	Severe depression (n=61)	5.1 ± 3.5	5.2 ± 3.6	0.939

Data are presented as mean±SD. P <0.05 was considered as statistically significant.

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Table 4. Correlation of biochemical parameters with anxiety and depression beck degree

Parameters	Anxiety sub-groups (n=77)	Beck.Anxiety r	Beck.Anxiety p
Vit B12 (pg/ml)	Mild Anxiety (n=18)	0.403	0.093
	Moderate Anxiety (n=59)	0.105	0.427
Folic Acid (ng/ml)	Mild Anxiety (n=18)	-0.144	0.57
	Moderate Anxiety (n=59)	0.215	0.102
Depression sub-groups (n=73)		**Beck.Depression r**	**Beck.Depression p**
Vit B12 (pg/ml)	Moderate depression (n=12)	0.056	0.871
	Severe depression (n=61)	0.106	0.418
Folic Acid (ng/ml	Moderate depression (n=12)	-0.322	0.332
	Severe depression (n=61)	-0.250	0.049*

r: Correlation coefficient

3.2. Correlation of vitamin B12 and folic acid concentration with Beck's depression/anxiety inventory scores

As it is presented, a significant negative correlation was observed between folic acid levels and BDI-II in severely depressed patients (r=-0.250, p=0.049). Univariate association and correlation between vitamin B12 and folic acid levels and Beck's inventory scores for depression and anxiety are presented in Table 4.

4. Discussion

The study aim was to evaluate the association of anxiety and depression with the levels of vitamin B12 and folic acid. We described higher levels of vitamin B12 in depressed males than female subjects with the same mood disorder. A lower level of serum folic acid in the depression group was observed compared to the anxiety group. Moreover, correlation analysis showed a significant negative correlation between folic acid levels and Beck's inventory score in severely depressive patients. This finding is similar to the results of a study conducted by Sanchez-Villegas et al. (Sánchez-Villegas et al., 2009).

Vitamin B12 and folic acid are critical for the development and the proper function of the nervous system in humans (Calderón-Ospina & Nava-Mesa, 2020). Conducted studies during the last decades have indicated an association of these vitamins' deficiencies with psychological symptoms, such as depression and cognitive impairment (Bottiglieri et al., 2000; Ford et al., 2008).

In an experimental study, Lerner et al. compared the serum concentations of vitamin B12 and folic acid in 224 newly diagnosed psychiatric patients and healthy controls in an Israelian population (Lerner et al., 2006). The results showed no significant differences between vitamin B12 levels within groups. In contrast, folate serum level was significantly higher in controls compared to patients with mood disorders. Moreover, a significant positive correlation was also observed between low folic acid levels and depression, consistent with our data. In a recent cross-sectional large cohort study on 7963 healthy Israelian individuals aged 18-65 years, Margalit et al. observed a significantly lower level of serum vitamin B12 in men compared to the women (Margalit, Cohen, Goldberg, & Krause, 2018). On the other hand, most of the examined population belonged to a higher socioeconomic class and may affect the external validity of the study by Margalit et al. Additionally, vitamin B12 deficiency prevalence in men was also higher. Nutritional, hormonal and social factors may partially clarify the obseved differences between the two genders.

Single nucleotide polymorphism (SNP) in the gene fucosyltransferase two have been associated with vitamin B12 absorption and serum level (Tanaka et al., 2009). Among the healthy population, men are susceptible to vitamin B12 deficiency. This can be explained by neither diet habits nor estrogen effects. Genetic variations involved in vitamin B12 homeostasis are therefore hypothesized to play a role. The lower serum vitamin B12 level in female severe depressive individuals in our study may explain the importance of this vitamin in mood disorders. Although the serum levels of vitamin B12 levels were low, they did not reach a "deficient" state in studied sub-groups.

Based on the previous studies reports, folic acid's role in mood disorders, including depression, seems to share a higher degree of importance. In a cross-sectional analysis was carried out by the National Health and Nutrition Examination Survey (NHANES) data, a non-causal association was observed between various serum vitamins (including vitamin B12 and folate) concentrations and depression in 2,791 individual (Huang et al., 2018) s. In this study, folate and vitamin B12 concentrations were also identified to be correlated with depression in the females.

In a double-blind, randomized controlled trial, depression scores were significantly reduced following combined treatment with 20 mg citalopram plus 2.5 mg folate when compared to controls (Sepehrmanesh et al., 2017). Furthermore, 73% of the patients receiving folate supplement had favorable response to citalopram, while only 40% of the patients in the control group demonstrated a favorable outcome to the treatment. The lower levels of folate in depressed patients and the negative association between folate and severe depression in our study may also confirm this vitamin's importance in mood disorders, especially depression.

Passeri et al. also compared the effects of 5'-methyltetrahydrofolate (50 mg/day) and trazodone (100 mg/day) in addition to standard psychotropic medication on depression and cognitive status in a double-blind design for eight weeks in an Italian population (Passen et al., 1993). In this study, a significant decrease in the Hamilton depression rating scale was observed

in patients supplemented with folate than the baseline, and the trazodone treated group after 4 and 8 weeks of intervention.

The association of low folate levels and poor response to selective serotonin reuptake inhibitors (SSRIs) has also been previously described in significant depression (Alpert et al., 2002; Papakostas et al., 2012). Papakostas et al. reported a higher efficacy of adjunctive 15 mg/day L-methyl-folate in combination with SSRI therapy compared to the placebo group for 60 days in both primary and secondary depression symptoms improvement. Similar results have also been reported from the United States (Alpert et al., 2002).

The limitations of our study include i) relatively small study population. A higher population may exert more confident results, particularly in anxiety patients. ii) Lack of a healthy control group and iii) the cross-sectional data. Other factors, including the duration of the vitamin B12 and folic acid deficiency, duration of psychiatric symptoms, lifestyle, and genetic variations, may also explain these relationships. Thus, further studies are still needed to examine the causal pathways between these vitamin deficiencies and mood disorders.

5. Conclusion

Based on our findings, Vitamin B12 and folic acid measurement may help the physicians for efficient anxiety and depression management. In this regard, folic acid seems to be more critical in mood disorders improvement outcomes and is suggested to be evaluated more carefully. Moreover, regarding the fact that the mean level of Vit B12 and folic acid were within typical values in this study, the need for treatment when no deficiency exists may be beneficial for better treatment outcomes.

Patient informed consent: Informed consent was obtained.
Ethics committee approval: This study was approved by the non-interventional research ethics committee at Uskudar University (Code: 61351342-/2019-80; date: 27.02.2019).
Conflict of interest: There is no conflict of interest to declare.
Financial support and sponsorship : No funding was received.
Author contribution subject and rate:
Habib Erensoy (%100): prepared the abstract, statistical analysis, and discussion.

The author gratefully acknowledges the assistance of Laboratory staff and the patients who collaborated with this study. The author declares no conflict of interest.

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